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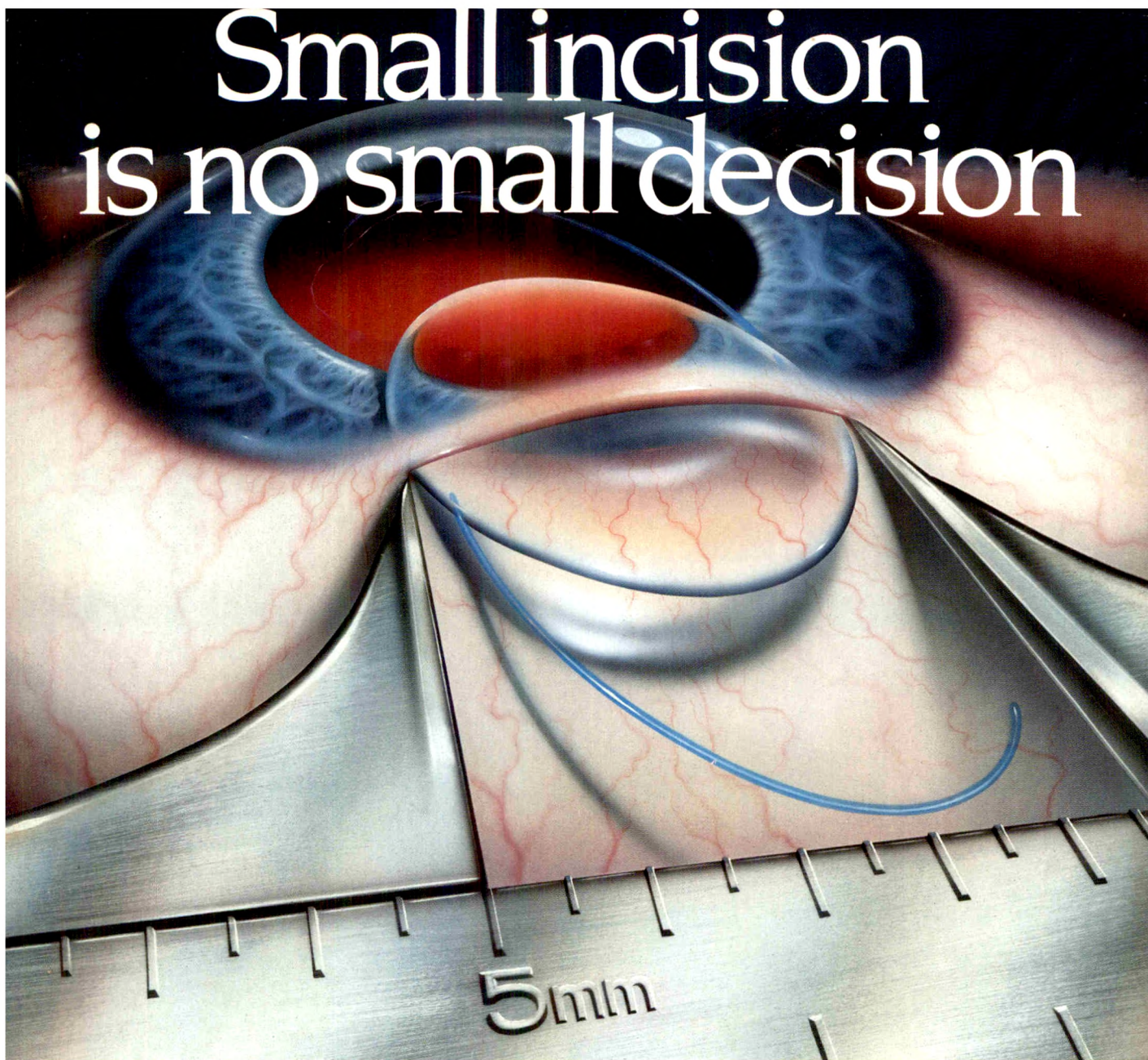
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Chorioretinal Degeneration in Infantile Malignant Osteopetrosis

James B. Ruben, M.D., Robert J. Morris, F.R.C.S., and G. Frank Judisch, M.D.

We studied two patients who had infantile malignant osteopetrosis, severe visual loss, and diminished electroretinogram amplitudes with visible macular chorioretinal degenerative changes. The findings support the hypothesis that a subgroup of patients with infantile malignant osteopetrosis exists in whom the visual loss is caused by a primary retinal degeneration that may be associated with generalized central nervous system neuronal degeneration.

Osteopetrosis describes a group of hereditary metabolic bone diseases characterized by increased skeletal mass caused by defective bone resorption. The diseases can be classified into two categories, juvenile-onset and adult-onset osteopetrosis. As many as four subtypes of each category have been described.[1]

The mild form of the disease, adult-onset, occurs later in life and is inherited in an autosomal-dominant manner. Many patients are asymptomatic, and the disease may be diagnosed incidentally after radiographic study. Such patients, however, may develop fractures, bone pain, and rarely cranial nerve palsies,[2] including optic atrophy.

Infantile malignant osteopetrosis is a subtype of the juvenile-onset category.[1,3] It is an autosomal-recessive disorder that develops in utero or in the first few months of life, and is lethal within the first decade of life if untreated.

Osteoclast dysfunction in all types of osteopetrosis[4,5] results in abnormal bone resorption, thickened cortical bone, structural skeletal defects, and frequent bone fractures. Narrowing of skull foramina can cause compressive cranial nerve damage. Crowding of the medullary space stimulates extramedullary hematopoiesis, with secondary hepatosplenomegaly, anemia, thrombocytopenia, leukopenia, and increased susceptibility to infection.

Neurologic manifestations of infantile malignant osteopetrosis are common and are often the first manifestation of the disease. They include extreme irritability, cranial nerve palsies, dysarthria, developmental delay, hydrocephalus, mental retardation, and cerebral atrophy.[6-8]

Ocular sequelae[3,6-9] are prominent, including optic atrophy, papilledema, nystagmus, strabismus, limitation of extraocular movements, and proptosis. Severe visual loss is usually associated with optic atrophy and is seen in about 80% of cases.[2] Although such visual loss was previously considered secondary to compressive skeletal disease, reports of abnormal retinal histopathologic[10] and electrophysiologic[11] characteristics suggest that, in some cases, a primary retinal degeneration may be responsible for the visual loss.

We studied two patients with infantile malignant osteopetrosis who had progressive macular chorioretinal degenerative changes and abnormal electroretinograms.

Case Reports

Case 1

A 7-week-old girl was admitted to our institution for failure to thrive and severe anemia. Her family history, gestation, delivery, and perinatal course were unremarkable.

Examination on admission disclosed an irritable infant with hepatosplenomegaly, anemia, leukocytosis, and thrombocytopenia. A chest X-ray showed increased bone density, and a bone survey showed diffusely sclerotic bone structures indicative of osteopetrosis. Bone marrow biopsy disclosed decreased erythropoiesis, granulopoiesis, and cellularity with increased trabecular structure, confirming the diagnosis of osteopetrosis. A computed tomographic scan of the head showed diffuse thickening and increased density of the skull bones with absence of the intramedullary space, and mild nonspecific enlargement of the ventricular system. A high-resolution orbital computed tomographic scan (Fig. 1) showed optic canals that measured 1 mm in greatest diameter (normal for age is at least 3 to 5 mm).[12,13]

Ocular examination showed no behavioral response to light. The pupils reacted sluggishly to light. Ophthalmoscopy disclosed bilateral central macular pigmentary changes with zones of geographic atrophy (Fig. 2). There was mild optic disk pallor. Both photopic and scotopic electroretinogram b-wave amplitudes were greater than 3 S.D. below normal. A bright-flash visual-evoked potential was nonrecordable in both eyes.

The patient's hospital course was characterized by extreme irritability, poor feeding, profound anemia, and thrombocytopenia. Bilateral facial and auditory nerve palsies developed. Computed tomography of the head one month after admission showed an increase in ventricular size and prominence of the sulci, which was believed to be consistent with cerebral atrophy. A bone-marrow transplant was precluded by general physical and neurologic deterioration. Eight weeks after admission, the child died. Permission for autopsy was denied.

Case 2

An 18-week-old boy with infantile malignant osteopetrosis was transferred to our institution for a bone-marrow transplant. Pregnancy, delivery, and family history were unremarkable. Severe anemia, thrombocytopenia, leukocytosis, and hepatosplenomegaly had been noted by 8 weeks of age. Results of a bone-marrow biopsy, skeletal survey, and computed tomography of the head were consistent with infantile malignant osteopetrosis.

Ophthalmologic examination disclosed aversion to light as the only visual response. The pupils reacted sluggishly to light. Searching, pendular, conjugate ocular movements were

Fig. 1 (Ruben, Morris, and Judisch). Computed tomographic scan of the optic canals in Patient 1. Optic canals (arrows) measure 1 mm in diameter.

present. Ophthalmoscopic evaluation disclosed moderate disk pallor with macular retinal pigment epithelial mottling (Fig. 3, left). Computed tomography of the orbit showed a generalized increase in bone density and narrowing of the optic canals. The photopic electroretinogram b-wave was 1.5 S.D. below normal, and the scotopic b-wave was 2 S.D. below normal. A bright-flash visual-evoked potential was nonrecordable in both eyes.

After induction with cytarabine, cyclophosphamide, and busulfan, the patient underwent bone-marrow transplantation, which failed.

Six months after bone-marrow transplantation, no change in visual response could be detected. Ophthalmoscopy disclosed pale optic disks and progression of the macular pigmentary retinopathy (Fig. 3, right).

Fungal sepsis ensued and the patient died. Permission for an autopsy was denied.

Discussion

The pathogenesis of visual loss and optic atrophy in osteopetrosis remains uncertain. Visual loss has been attributed to optic nerve compression by a narrowed optic canal,[8,9,14-16] failure of normal optic nerve myelinization,[17] primary retinal degeneration,[10,11] hydrocephalus,[8] and long-standing papilledema.[8]

Visual loss in osteopetrosis is frequently associated with radiographic evidence of narrowing of the optic canal,[7,9,18] and attempts at surgical decompression of the optic nerve may result in improved visual function[7,14,16] or continued deterioration of vision.[7,11,19-21] Most investiga-
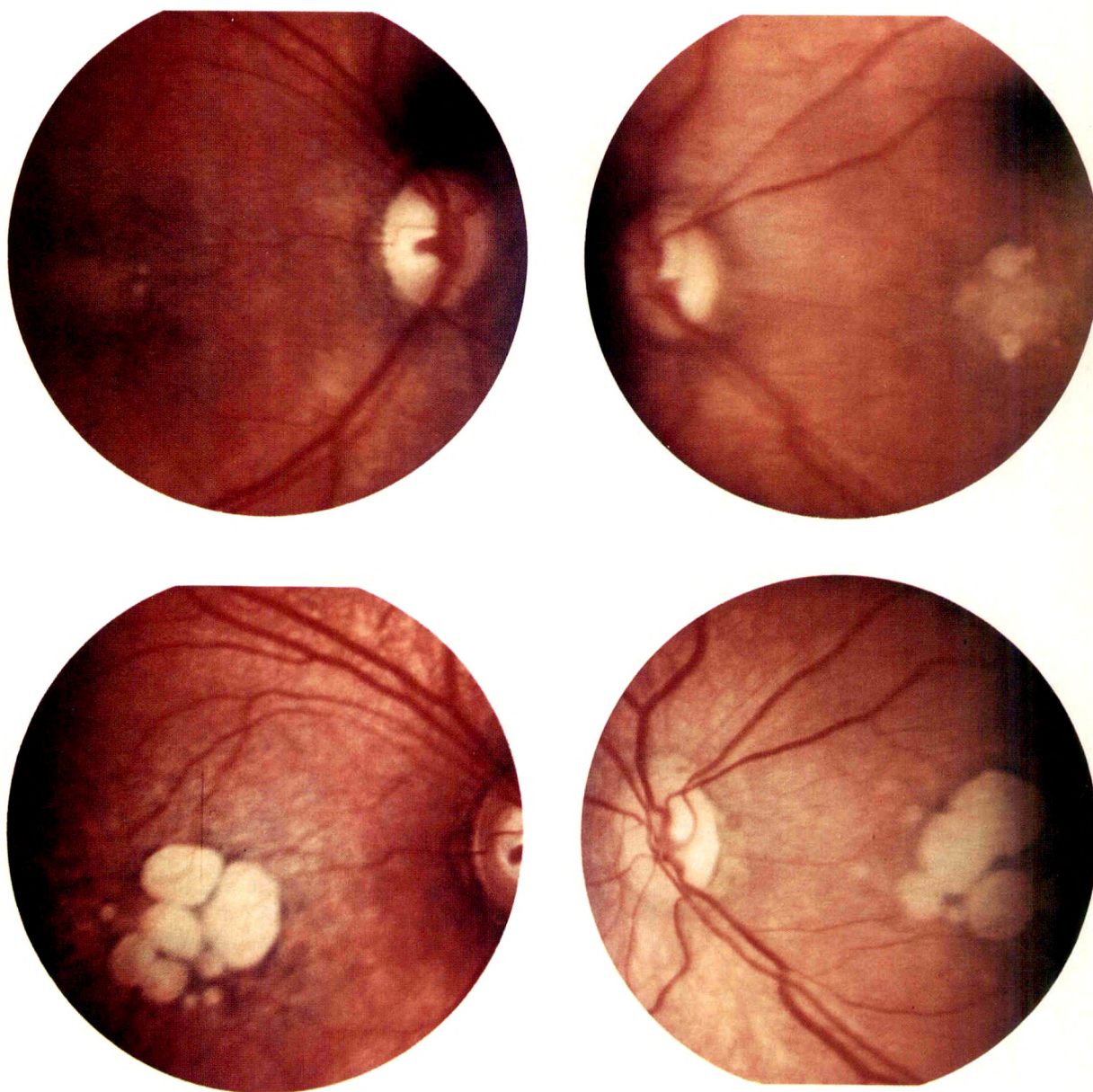
Fig. 2 (Ruben, Morris, and Judisch). Patient 1 at 7 weeks of age. Optic nerve pallor and early retinal pigment epithelial changes in the right eye (top left) and left eye (top right) are shown. Marked progression of macular degeneration at 13 weeks of age in the right eye (bottom left) and left eye (bottom right).

tors who report surgical results fail to distinguish the relatively benign adult form and the more malignant infantile form of the disease. Such studies must be interpreted cautiously because the pathogenesis of visual loss may vary depending on the patient's genotype.

The visual loss in some patients with osteopetrosis has been ascribed to nonskeletal factors. Keith[10] described a patient who had histopathologic findings of prominent inner and outer retinal degeneration in the central fundus. The results of this patient's antemortem ophthalmoscopic fundus examination were normal and showed no evidence of optic nerve compression. Hoyt and Billison[11] described three patients who had electrophysiologic evidence of diffuse retinal dysfunction in the absence of significant visible signs of retinal degeneration. Although all three patients had clinically apparent optic nerve pallor, only one patient had sufficient optic canal narrowing to cause optic nerve compression. The electroreti-
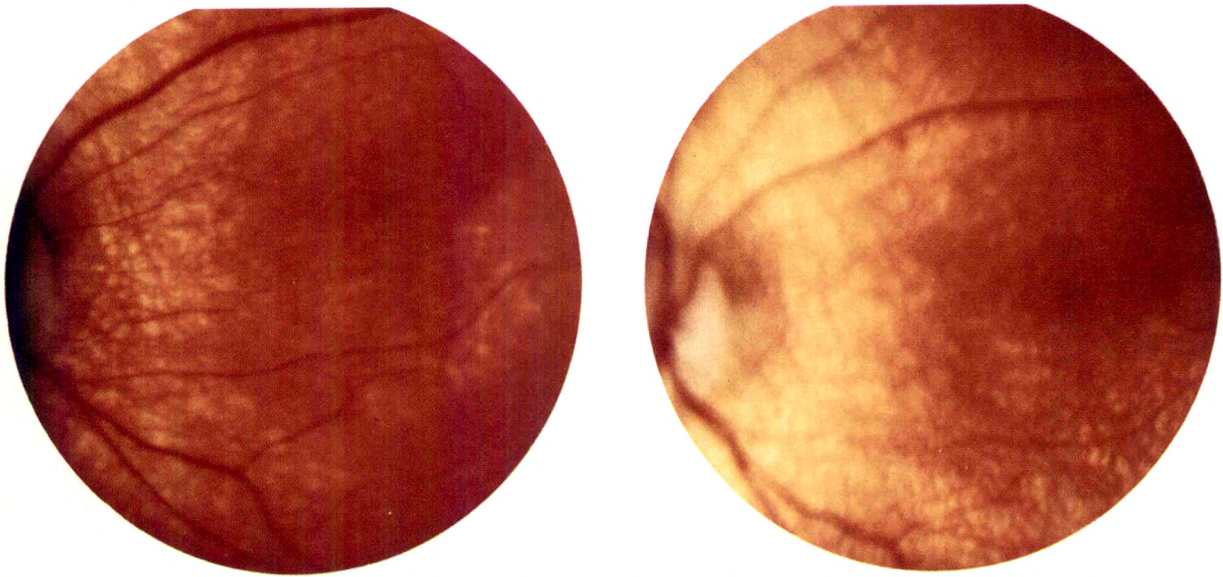
Fig. 3 (Ruben, Morris, and Judisch). Left, Left eye of Patient 2 at 4½ months of age. Chorioretinal atrophy in the posterior pole is shown. Right, Left eye of Patient 2 at 8 months of age. Progressive atrophy of macula and peripapillary retinal pigment epithelium is shown.

nographic findings in our patients are similar to those of Hoyt and Billison,[11] but the bright-flash visual-evoked potential was nonrecordable in our patients and was variably but significantly reduced in all of their patients. Additionally, our patients developed progressive visible macular chorioretinal degenerative changes. It is uncertain if the nonrecordability of the visual-evoked potential in our patients was a manifestation of their progressive macular degeneration, compressive optic neuropathy, or a combination of both of these factors.

Hydrocephalus in osteopetrosis may result from obstruction of the cerebral venous outflow secondary to narrowed venous foramina.[8] Lehman and associates[6] dispute this hypothesis and suggest that the cause of the observed cerebral atrophy is primary central nervous system parenchymal disease. Several recent autopsy studies also suggest the coexistence of a degenerative neuronal dystrophy with infantile malignant osteopetrosis. Histopathologic study of the brains of a stillborn and several live-born infants who later died has shown widespread axonal dystrophic changes with numerous spheroidal bodies.[6,22,23]

Two brothers with infantile malignant osteopetrosis, cerebral atrophy, ventricular dilation, neuronal loss, astrogliosis, and axonal spheroids have been described.[24] Lipofuscin-positive material was present in all neuronal elements in the brainstem, spinal anterior horn cells,

cerebral cortex, subcortical nuclei, and cerebellum. Examination of one patient's eye disclosed evidence of astrogliosis in the outer retinal layers.

The recent association of infantile malignant osteopetrosis with a neuronal storage disease, and the observation of abnormal electroretinograms and degenerative retinal changes in a subset of patients with this disease, suggest that visual loss in certain patients may be secondary to a coexistent neuronal storage disease. This hypothesis is particularly attractive because lysosomal dysfunction has been described in both infantile malignant osteopetrosis and neuronal storage disorders.[24,25]

The basic osteoclast defect in osteopetrosis can be reversed by transplantation of normal donor hematopoietic stem cells.[26,27] Bone marrow transplantation in several patients has been successful not only in reversing the skeletal and hematologic abnormalities,[6,19,21] but also in improving electroretinographic results and visual function.[28] Decompression of a compressed optic nerve is still advocated in these patients, because constriction of foramina is reversed slowly after bone-marrow transplantation.[3]

Determining the cause of visual loss in a patient with infantile malignant osteopetrosis is essential for proper management of the disease. Optic canal patency should be investigated with a high-resolution computed tomogra-

phy of the orbit or an optic neurogram.[18] A computed tomographic scan or magnetic resonance imaging scan of the brain should be obtained to evaluate for generalized neurodegenerative changes. Finally, electroretinography and careful ophthalmoscopic examination should be performed to determine if a primary retinal degeneration is present. Patients with radiologic and clinical signs of optic nerve compression in the absence of an overlying primary retinal degeneration appear to be the best candidates for decompressive surgery.

The progressive ophthalmoscopic changes described herein corroborate electrophysiologic and histopathologic evidence for a progressive primary retinal degeneration in at least some patients with infantile malignant osteopetrosis. These findings suggest that the retinal dysfunction may be associated with a generalized central nervous system degeneration. Additional studies are indicated to clarify the mechanisms of visual loss in this clinically diverse and genetically heterogeneous disease.

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Ocular Involvement in Patients With Onchocerciasis After Repeated Treatment With Ivermectin

Aniki Rothova, M.D., Allegonda Van der Lelij, M.D., Jan S. Stilma, M.D., Nynke Klaassen-Broekema, M.D., William R. Wilson, M.D., and Robert F. Barbe, M.D.

We assessed ocular changes after therapy at six and 12 months with ivermectin (150 μg/kg of body weight) in a 12-month prospective study of 29 patients with ocular onchocerciasis and 15 patients with onchocerciasis without ocular involvement. The patients lived in a hyperendemic area in Sierra Leone, West Africa, where no vector control was instituted. Five months after initial treatment, the microfilarial load in skin and eyes had decreased significantly (P < .0000), but 28 of 44 (63%) patients had positive skin-snip test results and nine of 29 (31%) patients with ocular involvement had active ocular disease. Twelve months after initial treatment, 15 of 41 (37%) patients had positive skin-snip test results and eight of 26 (31%) showed active ocular involvement. All patients with persistent ocular disease after therapy showed evidence of active onchocerciasis at that time, which suggests that a dose of ivermectin at six-month intervals is not sufficient for intensely infested patients with severe ocular disease. We developed an ocular involvement score to evaluate the patient's total ocular status and observed a significant relation between the pretreatment severity of ocular involvement and the persistence of active ocular disease after treatment with ivermectin.

ONCHOCERCIASIS or river blindness is a major and preventable cause of blindness. About one million people are blind or have a severe visual handicap as a result of this parasitic infection; more than 80 million people live in endemic areas and are therefore at risk for this disease.[1] Onchocerciasis is found mainly in medically underprivileged areas and has received little attention from medical scientists, despite the enormity of the problem.

Onchocerciasis is caused by the filarial worm, *Onchocerca volvulus*. The adult worms produce large numbers of microfilariae in the human host, and the death of these microfilariae is the major cause of the ocular disease. Ocular involvement includes the presence of either living or dead microfilariae in the eye, which results in corneal disease (punctate keratitis, snowflake opacities, sclerosing keratitis), iridocyclitis (frequently associated with secondary cataract and glaucoma), chorioretinal alterations, and optic neuritis and disk atrophy.

For many years, specific therapy for onchocerciasis, which was limited to diethylcarbamazine and suramin, was frequently complicated by severe adverse systemic and ocular reactions because of the massive death of the microfilariae.[2-7] An aggravation of the ocular disease associated with diethylcarbamazine therapy includes an increase in microfilariae in the cornea and therefore a marked increase in punctate corneal opacities.[8] Of particular importance are irreversible posterior segment changes, sometimes associated with permanent visual loss, as described by Bird and associates.[9]

A new agent in the field of onchocerciasis therapy is ivermectin. Ivermectin was reported to be safe for patients with ocular onchocerciasis.[10-16] After the administration of ivermectin, usually only short-term mobilization of microfilariae into the anterior chamber or mild anterior uveitis were observed.[11,13,16] Active infiltrates in already damaged retinal areas after ivermectin therapy were observed in three severely infected patients with extensive ocular

involvement.[17] The purpose of this study was to evaluate the long-term efficacy of ivermectin therapy (five and 12 months after treatment) in a severely infected population from Sierra Leone, West Africa, where no vector control was applied.

We observed a clear relation between the pretreatment severity of ocular involvement and the persistence of active ocular disease after repeated treatment with ivermectin.

Patients and Methods

A total of 48 onchocerciasis patients were studied. Group 1 consisted of 31 patients with ocular onchocerciasis (children younger than 12 years of age and pregnant or lactating women were excluded) who consulted the Eye Hospital Lunsar and were living within 20 km of the hospital. Although it was intended that the patients would represent consecutive ocular onchocerciasis cases from Eye Hospital Lunsar (except the patients with two atrophic eyes), it is probable that a referral to us formed a selection of patients with severe ocular involvement. Group 2 included 17 members of the hospital staff who had onchocerciasis but no ocular involvement. Of 48 onchocerciasis patients, four missed the five-month examination (two with and two without ocular involvement); therefore, 44 patients were studied. At the 12-month examination, three additional patients with ocular onchocerciasis were absent; one patient died and two others left the area and could not be located. The male:female ratio in this series was 3:1, and the mean age was 42 years (range, 12 to 71 years).

The diagnosis of onchocerciasis was based on the skin-snip test. Microfilariae were counted three minutes after skin snips were taken with a needle and razor blade from the iliac crest.[17] The severity of parasitic infestation was determined according to the skin-snip microfilariae count. Whenever the result was negative, a Mazzotti test with 50 mg of diethylcarbamazine was performed.[18]

The diagnosis of ocular onchocerciasis was based on the presence of either microfilariae in the eye or ocular lesions typical of onchocerciasis in patients with positive skin-snip test results. Active ocular onchocerciasis was diagnosed if intraocular microfilariae or active retinal infiltrates, or both, were observed.

All patients were treated with ivermectin in a single dose (150 μg/kg of body weight) according to the manufacturer's recommendations. Treatment was repeated at six and 12 months after the ophthalmologic examination and the skin tests had been performed.

All subjects received a complete ophthalmologic examination before treatment and five and 12 months after the start of treatment. The examination was performed according to the recommendations of the World Health Organization and included visual acuity testing with an illiterate-E chart, slit-lamp examination, ophthalmoscopy, posterior pole evaluation with a 90-diopter lens, and intraocular pressure measurements. Anterior segment photographs were taken in all patients, and fundus photographs were obtained whenever the fundus could be visualized through the camera. The ocular reaction index for anterior segment activity was determined as described by Keyvan-Larijani, Newland, and Taylor.[19]

An ocular involvement scoring system was developed that would reflect all (including irreversible) ocular changes caused by onchocerciasis (Table 1). The scores were determined by the sum of the scores for the total number of microfilariae in the cornea and the anterior chamber and the severity of sclerosing keratitis, anterior uveitis, chorioretinal changes, and optic nerve atrophy. Sclerosing keratitis consisting of nasal and temporal encroachment received one point (Fig. 1), confluent semilunar corneal opacities with a free pupil aperture received two points (Fig. 2), and confluent keratitis with covered pupil was rated 10 points (Fig. 3). Posterior segment changes consisting of subtle pigment epithelial alterations, sometimes in combination with punctate dots and cotton-wool spots, received one point (Fig. 4). Focal retinal atrophy was rated as two points (Fig. 5) and diffuse chorioretinal atrophy as three points (Fig. 6). We gave one additional point if the major retinal vessels were sheathed (Fig. 7) or if active retinal infiltrates (Fig. 8) or intraretinal microfilariae were present. When fundus photographs were available, we used them to determine the points for chorioretinal changes. The evaluation of fundus photographs was performed by two ophthalmologists in a masked manner. The points for each eye were added to determine the patient's score.

Statistical analysis was performed by using the chi-square test or Fisher's exact test when appropriate. Differences between the groups over time were compared by the parametric t-test for repeated measurements.

TABLE 1

OCULAR ONCHOCERCIASIS INVOLVEMENT SCORE

RATING (POINTS)	MICROFILARIAE IN ANTERIOR CHAMBER OR CORNEA (N)	SNOWFLAKE OPACITIES (N)	ANTERIOR UVEITIS (CELLS)	SCLEROSING KERATITIS	CHORIORETINAL CHANGES	OPTIC DISK INVOLVEMENT	RETINAL MICROFILARIAE OR ACTIVE INFILTRATES	SHEATHING OF MAIN RETINAL VESSELS
0	0	0	0	None	None	None	Absent	Absent
1	1–19	1–19	1–19	Nasal and temporal encroachment	Early pigment epithelium alterations	Papillitis or partial atrophy	Present	Present
2	20–50	20–50	20–50	Confluent, pupillary area free	Focal areas of atrophy with pigment clumps	Total atrophy	—	—
3	>50	>50	>50	—	Extensive atrophy	—	—	—
10	—	—	—	Confluent, pupillary area covered	—	—	—	—

Results

All patients with ocular onchocerciasis had positive skin-snip test results. Of the patients without ocular involvement, two had negative skin-snip test results; these two patients, however, had positive Mazzotti test results.

Fifty-five eyes of 29 patients with ocular onchocerciasis had ocular involvement. The posterior segment in five of these 55 eyes could not be evaluated accurately because of corneal and lens opacities. Fifteen patients (25 eyes) had chorioretinal changes, and 13 patients (21 eyes) had partial or total optic nerve atrophy.

Visual acuity of less than 20/200 was found in 21 of 55 (38%) affected eyes and less than 20/60 for 11 additional eyes (20%). In 15 of 21 eyes (71%), visual acuity of less than 20/200 was attributed to chorioretinal alterations or optic nerve atrophy or both. Four eyes had not only optic disk atrophy and chorioretinal changes involving the macular area but also glaucoma. Sclerosing keratitis involving the pupillary area was so extensive in three eyes that it was impossible to assess the posterior pole in detail. Visual loss because of cataract was observed at the initial examination in four eyes; lens extraction was performed in two of these eyes. In one eye, visual acuity improved to 20/20 after surgery; in the other eye, extensive retinal atrophy became visible after surgery, and visual acuity remained hand motions only.

Five months after treatment with ivermectin, skin-snip microfilarial counts were significantly lower than before therapy (P < .0000; Fig. 9). Eight of 29 (28%) patients with ocular onchocerciasis and eight of 15 (53%) patients without ocular involvement had negative skin-snip test results (difference not significant). All 12 patients with pretreatment microfilarial counts above 50 microfilariae per skin snip continued to have positive test results; however, their counts were lower than before treatment.

The number of eyes with microfilariae in the anterior chamber, snowflake opacities, and iritis was significantly reduced compared with those before treatment (P < .0000, P < .001, and P < .001, respectively; Table 2). Sclerosing keratitis, which involved nine eyes, remained stable.

Posterior segment changes are shown in Table 3. Seventeen of 25 (68%) eyes with retinal involvement remained unchanged. Six eyes (24%) showed either progression or active retinal infiltrates (Fig. 8). In the two remaining eyes, the subtle small areas of chorioretinal changes present before treatment were no longer present at the five-month examination. In two eyes, partial optic disk atrophy increased. In one patient, it occurred simultaneously with retinal deterioration.

A marked decrease in visual acuity occurred in four of 55 (7%) eyes (three patients). These eyes showed a progression of chorioretinal alterations. An increase in visual acuity from hand motions to 20/20 was observed in one
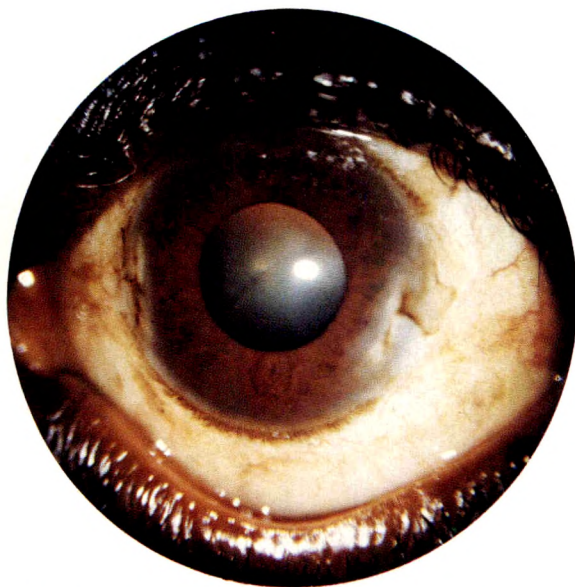
Fig. 1 (Rothova and associates). Sclerosing keratitis. Temporal and nasal encroachment.
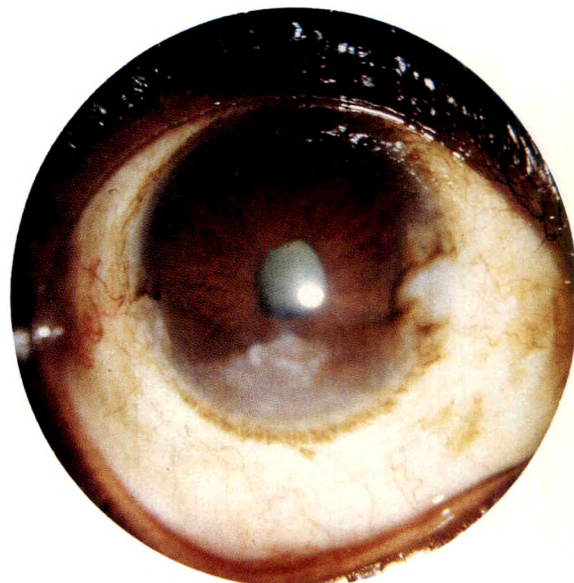
Fig. 2 (Rothova and associates). Sclerosing keratitis. Confluent semilunar opacity with a free pupil aperture.

patient after cataract extraction. In one eye with extensive retinal involvement, a pretreatment visual acuity of counting fingers improved to 20/60, probably because of resolution of retinal edema.

After five months, nine of 29 (31%) patients with ocular involvement (15 of 55 affected eyes,

27%) still showed active ocular disease (Fig. 9). All patients except one had positive skin-snip test results. The patient with active ocular disease and a negative skin-snip test result, however, showed a strong Mazzotti-reaction after the administration of a second dose of ivermectin.
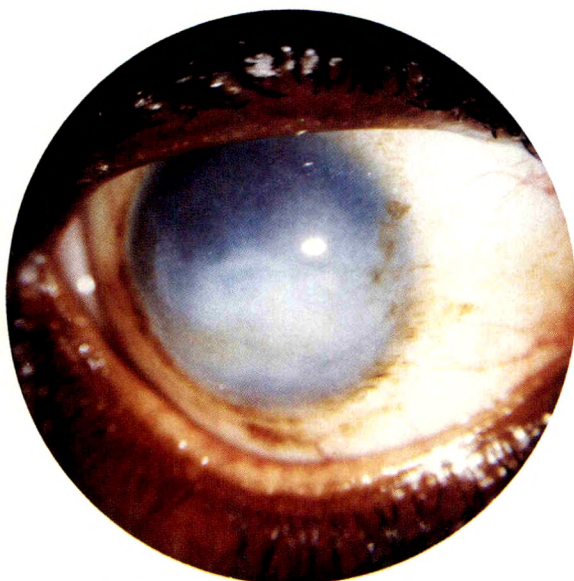
Fig. 3 (Rothova and associates). Sclerosing keratitis. Confluent opacity with a covered pupil aperture.

Fig. 4 (Rothova and associates). Chorioretinal changes in onchocerciasis, grade 1. Irregular atrophy of pigment epithelium shows mottled appearance.
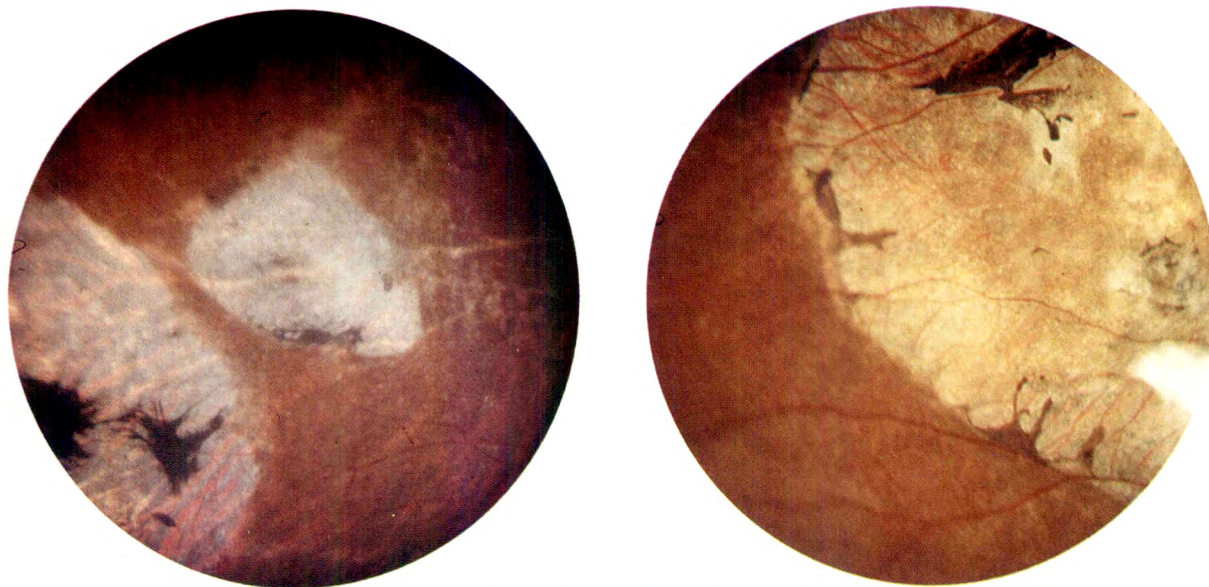
Fig. 5 (Rothova and associates). Chorioretinal changes in onchocerciasis, grade 2. Left, Multifocal atrophy of pigment epithelium and choriocapillaris with pigment clumping. Large choroidal vessels are visible. Right, Sharp demarcation of an atrophic area.

The ocular reaction index for the anterior segment and the ocular involvement score (Fig. 10) decreased significantly (P < .0000) after therapy.

All patients except one with an ocular involvement score above 10 showed intraocular microfilariae or retinal infiltrates, or both, at the five-month examination (P < .0000; Fig. 10).

Twelve months after the initial treatment with ivermectin (before the third dose), the skin-snip test result remained positive in 15 of 41 patients (37%), which is not significantly different from the results obtained at the five-
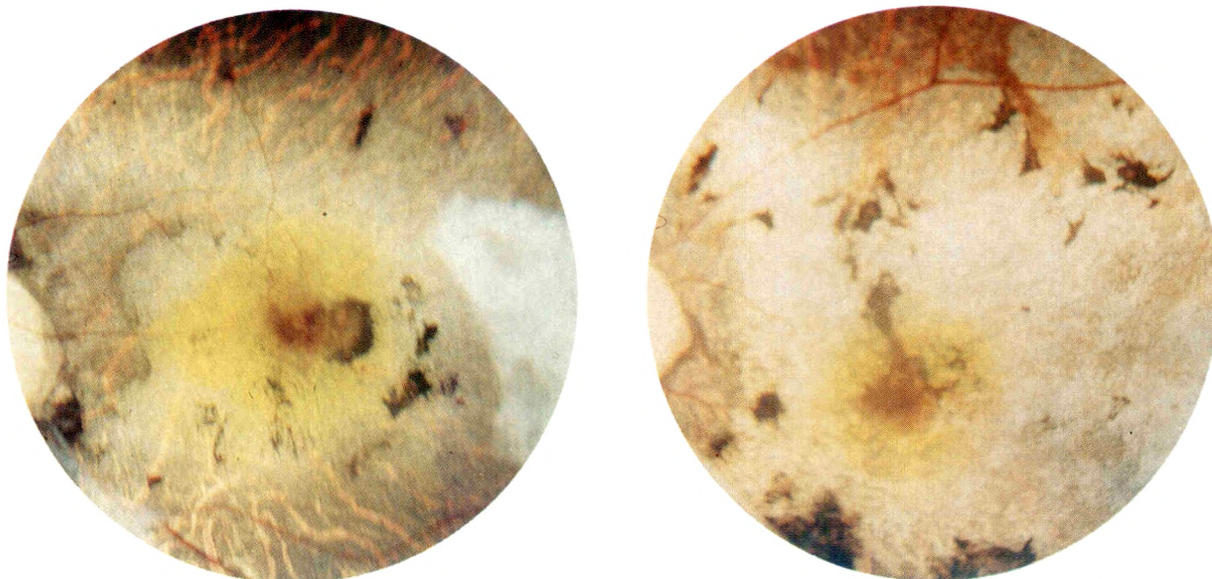
Fig. 6 (Rothova and associates). Chorioretinal changes in onchocerciasis, grade 3. Left and right, Diffuse chorioretinal atrophy with pigment clumping. Left eyes of two different patients.
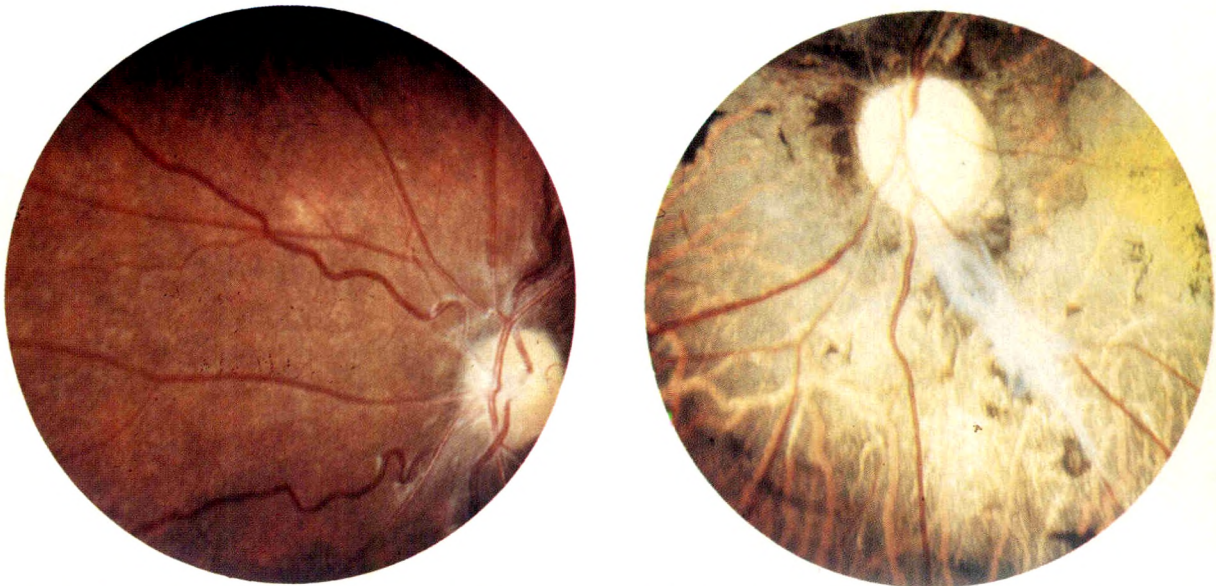
Fig. 7 (Rothova and associates). Sheathing of major retinal vessels in onchocerciasis. Left, Sheathing without major retinal changes. Right, Sheathing associated with extensive chorioretinal alterations.

month examination (Fig. 9). Twelve of 26 (46%) patients with ocular involvement and three of 15 (20%) of the patients without ocular disease had a positive skin-snip test result (difference not significant). Of the 12 patients with pre-treatment microfilarial counts above 50 microfi-lariae per skin snip, seven had positive results at the 12-month follow-up examination.

At the 12-month examination, the number of eyes with microfilariae decreased further to 12% (six of 49), and anterior uveitis remained absent (Table 2). We observed a reappearance

Fig. 8 (Rothova and associates). Active retinal infiltrates in onchocerciasis. Two eyes of two different patients. All infiltrates had indistinct, fluffy margins, sometimes associated with overlying vitreal cells. Left, Active retinal infiltrate five months after therapy with ivermectin. Right, Large infiltrate in atrophic retinal area.
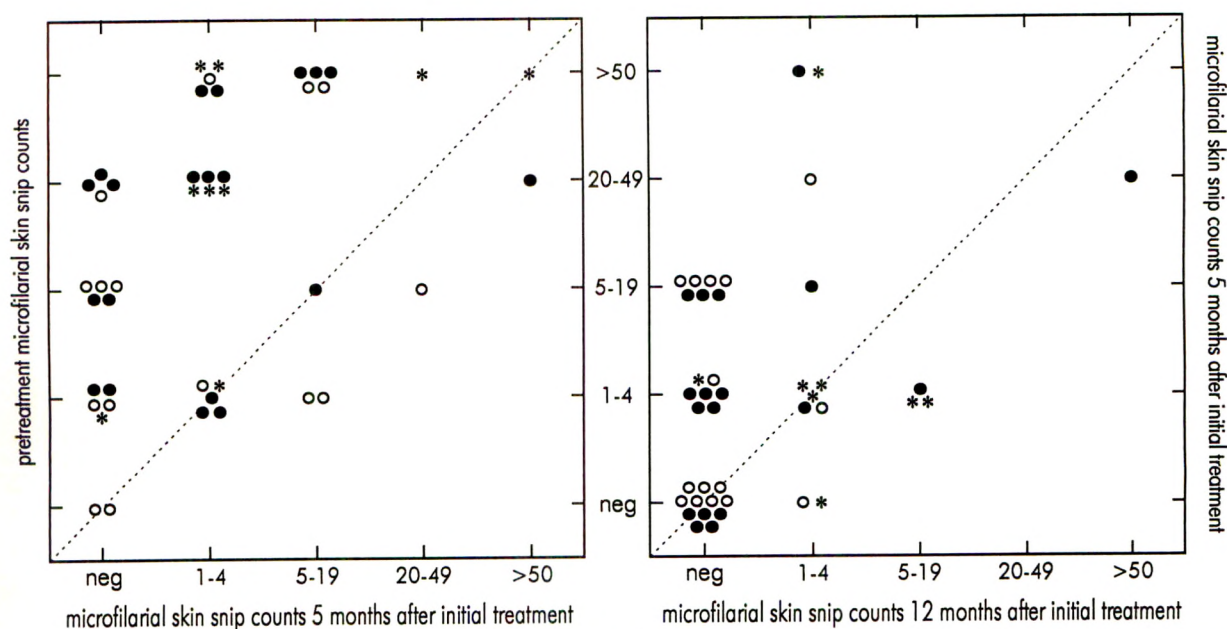
Fig. 9 (Rothova and associates). Effect of ivermectin therapy on parasitic infestation. Open circles indicate nonocular onchocerciasis patients; closed circles, ocular onchocerciasis patients, eye disease inactive after therapy; asterisks, ocular onchocerciasis patients, eye disease active after therapy.

of discrete snowflake opacities in three eyes. Three of the nine eyes with sclerosing keratitis showed improvement. These three patients had the early stages of corneal disease. In one eye, which was initially classified as negative for sclerosing keratitis, we noticed early corneal changes at the 3 and 9 o'clock meridians (this patient had positive skin-snip test results).

After two doses of ivermectin, 17 of 22 eyes with chorioretinal alterations remained stable. Two eyes with early retinal involvement showed regression. The conditions of three eyes with extensive chorioretinal changes, which had progressed at the five-month examination, showed further deterioration. No changes were noticed in optic nerve involvement and on retinal vessels when compared to the five-month examination. At the 12-month follow-up examination, there were no changes in visual acuity of affected eyes as compared to the five-month examination.

After 12 months, eight of 26 (31%) patients with ocular involvement (eight of 47 affected eyes, 17%) showed active ocular onchocerciasis (Fig. 10). All except one of these patients had positive skin-snip test results (Fig. 9). The patient with negative skin-snip test results had microfilariae in the anterior chamber of one of his eyes and also showed progression of his chorioretinal involvement. It is likely that the

skin-snip test gave a false-negative result in this patient.

Between the five- and 12-month examinations, the mean ocular reaction index and the mean ocular involvement score (Fig. 10) did not change significantly.

Discussion

A discussion of onchocerciasis treatment should address both infected patients under hospital supervision and control of the disease within a community. The latter is currently approached by vector control programs in combination with an annual dose of ivermectin, which has been found to be effective in interrupting transmission of *Onchocerca volvulus* for extended periods of time.[20,21] Our study concerns intensely infected patients with severe ocular involvement and shows that even a dose of ivermectin every six months is not sufficient to effectively control the microfilarial load in the skin and eyes of these patients.

After a single oral dose (150 μg/kg of body weight) of ivermectin, the microfilarial densities in the skin and eyes remained low for up to one year, probably because of the combination of a microfilaricidal effect and an impact on the

TABLE 2

EFFECT OF IVERMECTIN THERAPY ON ANTERIOR SEGMENT INVOLVEMENT IN AFFECTED EYES

	BEFORE TREATMENT (N = 55)		5 MOS AFTER TREATMENT (N = 55)		12 MOS AFTER INITIAL TREATMENT (N = 49)	
	N	%	N	%	N	%
Snowflake opacities	12	22	0	0	3	6
Microfilariae in anterior chamber	43	78	8	15	6	12
Anterior uveitis	12	22	0	0	0	0

release of microfilariae from an adult worm uterus.[11-13] In a longitudinal study of patients, the ocular microfilarial load decreased slowly after a single dose of ivermectin, (in some cases microfilariae disappeared after several weeks), and remained low for up to one year.[14,15] In another series, the number of ocular and skin microfilariae decreased significantly six months after ivermectin treatment; however, at one year no differences between the placebo and the treated group were observed.[22] These studies included mostly patients with mild ocular disease. These findings are important for community-based programs but do not indicate how to treat an individual patient with severe ocular disease.

Our results show that two thirds of all patients had positive skin-snip test results five months after therapy with ivermectin. After a second dose (at the 12-month examination), one third of the patients still had positive skin-snip test results. Our method of skin-snip testing is simple and convenient in the field; it does not, however, allow the quantification of the exact number of microfilariae per milligram of skin. False-negative test results were probably present in this series, because the number of microfilariae found in the skin snip after three minutes is undoubtedly lower than the number

that would have been obtained after incubation in a medium overnight.[23] This indicates that the number of patients with positive skin-snip test results after therapy might be even higher than the percentages given.

There is no consensus concerning the best therapy for individual patients, especially those who have severe ocular involvement and are at risk to become blind. In all of the mentioned studies, neither significant exacerbation nor progression of posterior segment involvement was observed after ivermectin use. The documented posterior segment changes after ivermectin therapy include temporarily increased disk hyperfluorescence without associated functional changes and transient or minor pigment epithelial changes.[12,13] The progression of disease after ivermectin therapy that was observed in our study could be explained by the severe infestation of our patients in combination with the absence of vector control in the area.

In this series, active ocular onchocerciasis despite treatment with ivermectin was observed during the follow-up period in 31% of patients. All of the patients with active ocular disease during follow-up showed evidence of parasitic infestation at that time. Our clinical findings suggest that retinal alterations can be attributed directly to microfilariae because the progression of retinal changes occurred only in patients with evidence of active onchocerciasis. This hypothesis is also supported by the adverse ocular reactions to microfilaricidal drugs, histologic evidence of microfilariae in the retina and choroid, and clinical observations of live intraretinal microfilariae.[24,25]

The persistence of positive skin-snip test results and active ocular involvement despite repeated treatment with ivermectin strongly suggest that treatment every 12 or six months with ivermectin (150 μg/kg of body weight) is not sufficient for patients with severe ocular disease. Until now, higher dosage regimens

TABLE 3

EFFECT OF IVERMECTIN THERAPY ON POSTERIOR SEGMENT INVOLVEMENT IN AFFECTED EYES

	BEFORE TREATMENT	5 MOS AFTER TREATMENT			
		NO CHANGE	IMPROVEMENT	PROGRESSION OR ACTIVITY	NEW CASES
Chorioretinal changes	25	17	2	6	0
Optic nerve involvement	21	19	0	2	0
Sheathing of main retinal vessels	10	10	0	0	1

Fig. 10 (Rothova and associates). Effect of ivermectin therapy on ocular involvement score. Mean ocular score: pretreatment examination, 7.48; five-month examination, 5.24; 12-month examination, 4.88.

progress, and new lesions frequently appear in other parts of the affected eye.[26-28]

Evaluation of posterior segment ocular changes caused by onchocerciasis is not consistent. In the past, little attention was directed toward the importance of optic atrophy and chorioretinal alterations as conditions potentially causing blindness in patients with onchocerciasis. Bird, Anderson, and Fuglsang[29] reported that optic nerve disease, alone or in combination with chorioretinal changes, was responsible for blindness in 88% of patients with posterior pole involvement in onchocerciasis.

The presence of posterior segment involvement indicates an advanced disease and may be important for the prognosis and the choice of the treatment. The irreversible ocular changes (such as chorioretinal scarring and optic disk atrophy) cannot improve with treatment, but preventing their progression is important because such changes determine the visual outcome.

We developed an ocular involvement score to evaluate the patient's ocular status (Table 1). This score combines onchocerciasis changes that involve the anterior and posterior eye segment. The score also attempts to evaluate the ocular disease in its entirety and give a more realistic view of ocular involvement in onchocerciasis. The evaluation of the posterior pole is impossible in a case of extensive sclerosing keratitis. In our study, a case of confluent sclerosing keratitis that involved the pupillary area received 10 points. Such advanced corneal involvement was reported not to lead to serious loss of visual acuity alone, but it is always combined with other ocular manifestations of the disease.[26]

The ocular involvement score proved to be highly predictive of the persistence of ocular disease activity and retinal deterioration. An ocular involvement score of 10 or more was strongly associated with active and progressive ocular disease five months after therapy with ivermectin ($P < .0000$) and can therefore be considered a poor prognostic sign. An assessment of the ocular status of a patient could be a valuable guide to treatment and may be important for the evaluation of new therapeutic regimens and agents in the course of their development.

We conclude that a dose of ivermectin (150 μg/kg of body weight) every six or 12 months is not sufficient to stop the progression of ocular

were not associated with better therapeutic results.[11,16] A schedule of more frequent dosages, however, has not yet been tested systematically in patients with ocular involvement. The possibility of a higher incidence of adverse reactions to such a regimen should also be anticipated.

The ocular reaction index, which evaluates only reversible changes in the anterior segment of the eye, is frequently used to monitor the effect of therapy.[19] Microfilariae in the anterior chamber of the eye decreased with ivermectin treatment in our patients with severe ocular involvement (Table 2). The presence of microfilariae in the anterior chamber predisposes the patient to the development of onchocercal eye lesions and visual deterioration; additionally, once an ocular lesion develops, it is likely to

disease in patients with severe eye involvement. Only future studies will provide conclusive evidence on the best therapy for ocular onchocerciasis.

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OPHTHALMIC MINIATURE

"Papa, have you lost your faith?"

"No."

Samantha asked me the questions as I stood by her bed. The neuroblastoma had pushed one eye out and around the nosebridge so she looked like a Picasso profile.

Walker Percy, *Love in the Ruins*
New York, Ivy Books, 1971, p. 319

Recurrent Conjunctival Papilloma Causing Nasolacrimal Duct Obstruction

Michael E. Migliori, M.D., and Allen M. Putterman, M.D.

We treated two patients who had recurrent conjunctival papillomas that invaded the nasolacrimal sac and caused complete canalicular and nasolacrimal duct obstruction. The ophthalmologist should be aware of the possibility of a conjunctival papilloma invading the lacrimal sac when treating patients with conjunctival papillomas. Excision should be complete, and adjunctive therapy such as cryotherapy should be considered to reduce the chance of tumor recurrence.

CONJUNCTIVAL SQUAMOUS PAPILLOMAS are typically benign lesions that develop on the conjunctival epithelium. They are often located in the inferior fornix but may develop anywhere on the conjunctival surface. Recurrence after excision is common, and a viral cause has been postulated. Squamous papillomas of the lacrimal sac are thought to be caused by a proliferation of reserve cells of schneiderian mucosa, a cause which is similar to that of papillomas of the nose and sinuses. Lacrimal sac papillomas are rarely associated with conjunctival papillomas.

We treated two patients who had recurrent conjunctival squamous papillomas that invaded the canaliculi and extended into the lacrimal sac, causing complete nasolacrimal duct obstruction. In one case, the papilloma showed mild to marked epithelial dysplasia within the lacrimal sac with no evidence of malignant transformation. The second case showed transformation of the papilloma from a squamous to a transitional cell type.

A case of a recurrent conjunctival papilloma invading the lacrimal sac and causing complete nasolacrimal duct obstruction has been described.[1]

Case Reports

Case 1

A 41-year-old man had a six-month history of epiphora and a recurrent medial canthal mass. The mass was first noticed and excised when the patient was 7 years old. The most recent recurrence and excision had been four years previously. The present lesion was the fourth recurrence. On examination, there was a 6 × 6 × 5-mm papilloma involving the caruncle and medial canthal tissue with subcutaneous extension (Fig. 1). Lacrimal irrigation was performed; there was some resistance to irrigation but no reflux, and the irrigated fluid passed into the nose. The lacrimal sac appeared to distend with irrigation. A dacryocystogram showed the lacrimal sac filled with tumor and a fistula to the medial canthus. The tumor was excised from the medial canthus and from within the

Fig. 1 (Migliori and Putterman). Patient 1. Initial appearance of recurrent medial canthal papilloma.
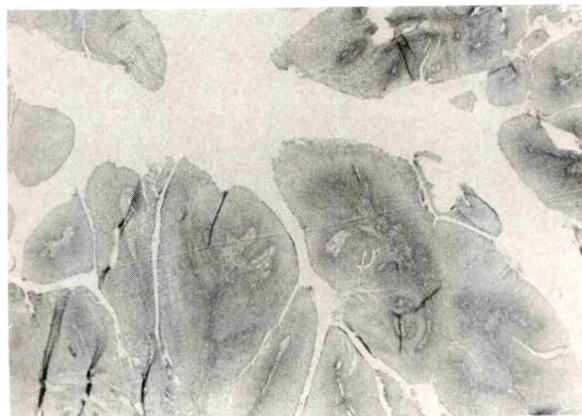
Fig. 2 (Migliori and Putterman). Patient 1. Pathologic specimen of excised papilloma shows typical fibrovascular fronds (hematoxylin and eosin, × 40).

Fig. 3 (Migliori and Putterman). Patient 1. Second recurrence of papilloma involving the medial canthus and lacrimal sac.

lacrimal sac. Cryotherapy to −20 C was applied to the involved tissue with a double freeze-thaw technique. A combination dacryocystorhinostomy-conjunctivodacryocystorhinostomy was performed with silicone intubation and placement of a glass Jones tube. The diagnosis based on pathologic evidence was squamous papilloma with moderate dysplasia in the portion of the tumor taken from the lacrimal sac (Fig. 2).

Six weeks later, there was an 8 × 6-mm recurrence on the medial upper eyelid not contiguous with the lacrimal sac. The Jones tube was removed, and cryotherapy to −20 C was applied to the medial eyelids and within the conjunctival ostium. This lesion was also found to be a squamous papilloma with mild focal dysplasia.

One month later, a recurrence of the mass was noted around the tube and extending into the nose (Fig. 3). Computed tomographic scans showed that the mass surrounded the Jones tube and extended through the bony ostium into the nose (Fig. 4). The medial upper and lower eyelids, canaliculi, and lacrimal sac were exenterated with wide surgical margins, and cryotherapy was applied (Fig. 5). This recurrence was also a squamous papilloma with
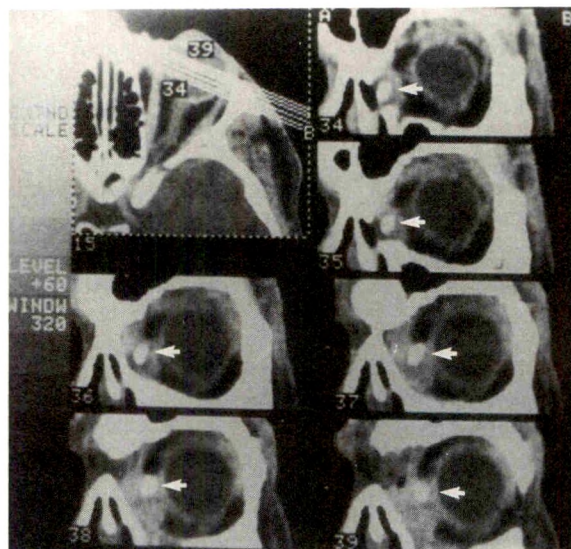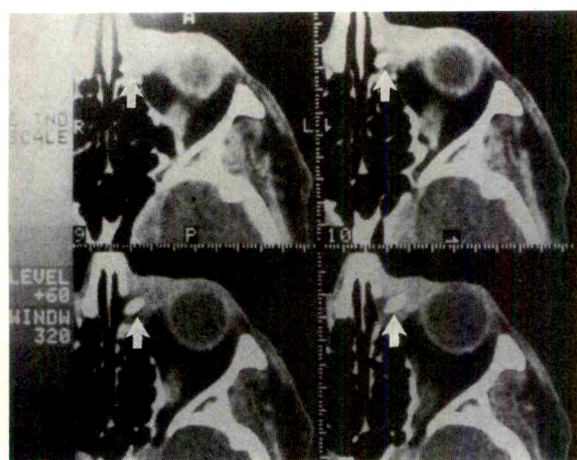
Fig. 4 (Migliori and Putterman). Patient 1. Computed tomographic scans show invasion of papilloma through lacrimal sac into the nose. Left, Axial scan. Note Jones tube in center of mass (arrows). Right, Coronal scan. Note Jones tube in center of mass (arrows).
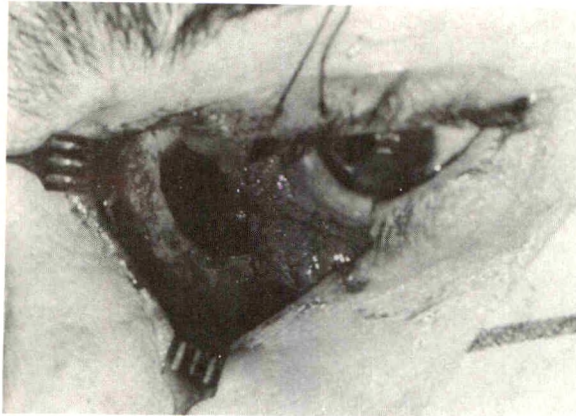
Fig. 5 (Migliori and Putterman). Patient 1. Intraoperative photograph shows exenteration of medial canthal tissue and lacrimal sac.

Fig. 6 (Migliori and Putterman). Patient 1. Pathologic specimen of recurrent lacrimal sac papilloma. Note koilocytosis (hematoxylin and eosin, × 100).

acute inflammatory infiltrate and extensive dysplasia. Koilocytosis was present in the lacrimal sac tumor (Fig. 6). There has been no recurrence in four years (Fig. 7).

Case 2

A 35-year-old woman had a recurrent papilloma on the nasal palpebral conjunctiva of her left upper eyelid (Fig. 8). She also had a history of verruca vulgaris of the skin. The eyelid lesion had been excised three times previously. The most recent excision and cryotherapy were performed three months before we examined the patient. The palpebral lesion measured 11 × 6 mm and was adjacent to the upper punctum. There was also a 5-mm papilloma at the inferior corneoscleral limbus. Both lesions were excised, and cryotherapy to −20 C was applied

with a double freeze-thaw technique. The diagnosis based on pathologic evidence was squamous papilloma.

Four months later, there was a 3.5 × 2.5-mm recurrence of the mass near the upper punctum. The patient returned seven months later complaining of epiphora. The lesion now measured 6 × 4 × 3 mm and covered the punctum. The papilloma was excised and cryotherapy repeated. The pathologic features were identical to those of the previous specimen.

Another recurrence eight months later obliterated the upper punctum, and probing of the lower punctum indicated that the tumor extended into the lower canaliculus. The lower canaliculus was slit open, and cryotherapy was
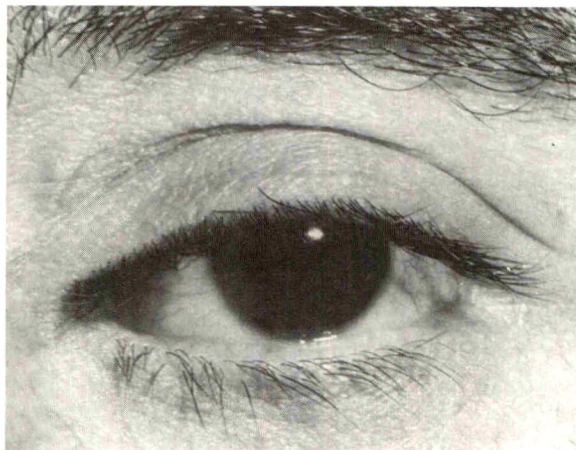
Fig. 7 (Migliori and Putterman). Patient 1. Postoperative appearance after medial canthal exenteration, cryotherapy, and reconstruction.

Fig. 8 (Migliori and Putterman). Patient 2. Initial appearance of recurrent papilloma on nasal palpebral conjunctiva of left upper eyelid.
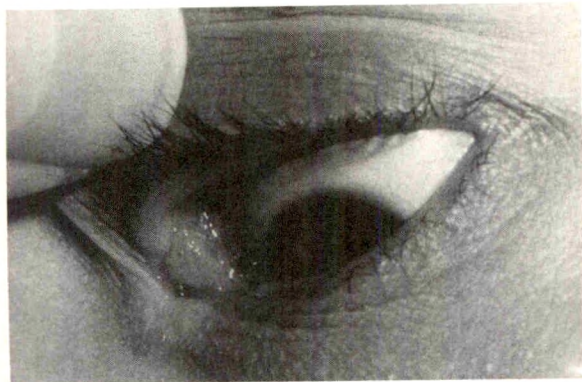
Fig. 9 (Migliori and Putterman). Patient 2. Second recurrence of papilloma 18 months after excision and cryotherapy.

applied directly to the tumor. The histologic features were again identical to those of the previous specimens.

The tumor recurred 18 months later (Fig. 9). Dacryocystography disclosed a mass in the lacrimal sac with complete obstruction of the nasolacrimal duct (Fig. 10). A dacryocystectomy was performed combined with cryotherapy to −20 C with a double freeze-thaw technique (Fig. 11). A conjunctivorhinostomy was then performed, and a Jones tube was inserted. The pathologic features of the tumor were those of a transitional cell papilloma (Fig. 12). A granuloma was excised from around the Jones tube several months later, but there has been no recurrence of the papilloma in 55 months of follow-up (Fig. 13).

Discussion

Squamous papillomas are typically benign lesions that develop from a focus of epithelial hyperplasia. They may occur on the conjunctiva, in the lacrimal sac, and in the nose and paranasal sinuses. Conjunctival lesions have been associated with verrucae of the skin and genitalia. A viral cause has been proposed for some conjunctival papillomas.[2,3]

Microscopically, these lesions may be composed of branching fronds that emanate from a pedunculated base. Each of these fronds has a central fibrovascular core, which is covered by an intact basement membrane and acanthotic, nonkeratinizing, stratified squamous epithelium. This growth pattern is termed exophytic and is the usual configuration of conjunctival papillomas.
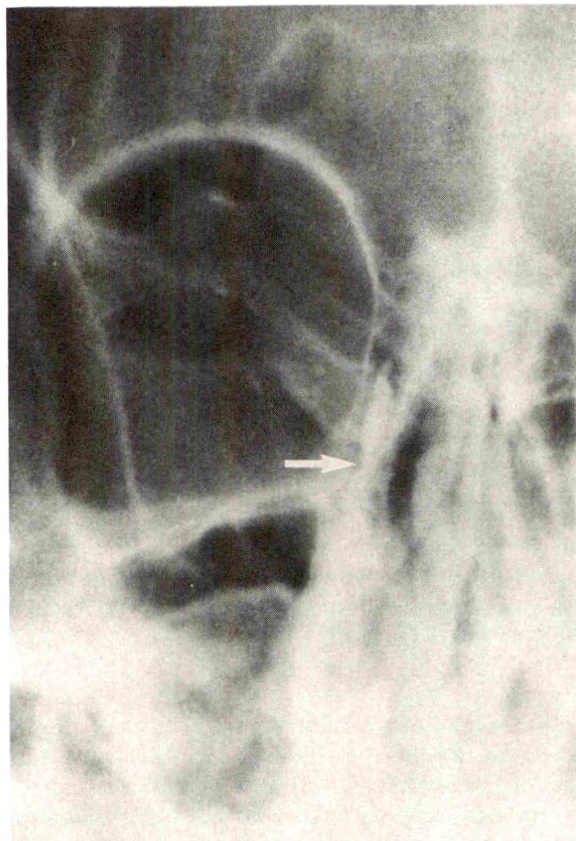
Fig. 10 (Migliori and Putterman). Patient 2. Dacryocystogram shows dilated lacrimal sac with filling defects and complete obstruction at the junction of the lacrimal sac and duct (arrow).

In inverted papillomas, areas of the acanthotic surface epithelium invade the stroma. Although rarely seen in conjunctival papillomas, this structure is more commonly seen in papillomas of the lacrimal sac, nose, and paranasal sinuses. This may be because of the confined space in which they are growing, which prevents exophytic growth and forces the proliferating epithelium to invade the underlying stroma. Occasionally, growth may be in a combination of exophytic and inverted patterns, which is termed a mixed pattern.

There is typically an orderly arrangement to the cells but there may be mild to severe atypia, dysplasia, or foci of carcinoma in situ.

Papillomas of the conjunctiva typically occur in children and young adults. They are usually unilateral and located in the inferior fornix but may also develop at the corneoscleral limbus, caruncle, or semilunar fold. They are rarely multicentric and may even be bilateral. Conjunctival papillomas have been seen in siblings[4]
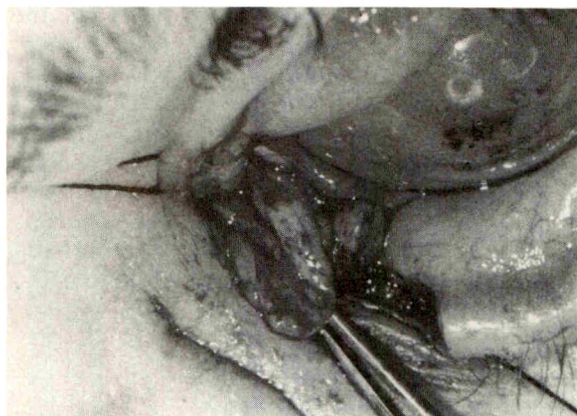
Fig. 11 (Migliori and Putterman). Patient 2. Left, Intraoperative photograph shows tumor filling the lacrimal sac. Right, Lacrimal sac with tumor excised.

and associated with verrucae of the skin. Lass and associates[2] reported that 24 of 40 conjunctival papillomas examined histologically showed koilocytosis typical of viral papillomas. Two of these lesions also had viral antigens.[3]

Conjunctival lesions usually exhibit an exophytic growth pattern, but there have been case reports of inverted conjunctival papillomas. Three cases of inverted papilloma of the conjunctiva reported by Streeten and associates[5] were unifocal and unilateral and did not recur after excision.

Canalicular papillomas are rare and are not usually associated with conjunctival or lacrimal sac lesions. Williams, Ilsar, and Welham[1] reported three cases of canalicular papilloma and reviewed 12 others. All were benign lesions, and all three of their cases were squamous papillomas. One patient was initially thought to have a conjunctival papilloma, but the tu-

mor recurred in the canaliculi and lacrimal sac. The cell structure in the lacrimal sac lesion remained squamous and did not transform into a transitional cell type as occurred in our Patient 2.

Benign epithelial papillomas constitute 40% of all neoplasms of the lacrimal drainage system. These lesions are most likely of the inverted type. They may be primary lesions or may develop on nasal or sinus mucosa.[6]

Ryan and Font[6] classified lacrimal sac papillomas by their cell type and growth pattern. They described three types: squamous cell papillomas consisting of acanthotic, stratified squamous epithelium; transitional cell papillomas, which are composed of stratified columnar epi-
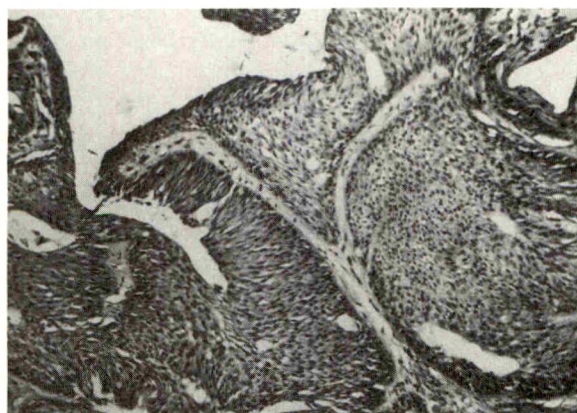
Fig. 12 (Migliori and Putterman). Patient 2. Pathologic specimen of lacrimal sac papilloma (hematoxylin and eosin, ×40).
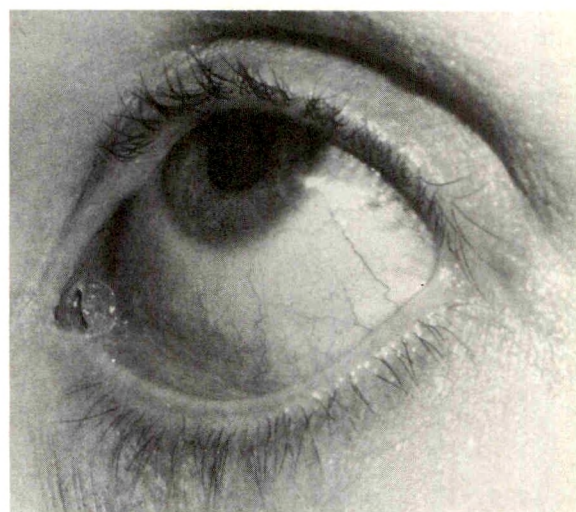
Fig. 13 (Migliori and Putterman). Patient 2. Postoperative appearance with functional Jones tube in place.

P 24,325

thelium with scattered goblet cells similar to normal lacrimal sac epithelium; and mixed cell papillomas, which show a mixture of squamous and transitional cell types. All three types of papilloma can have exophytic, inverted, or mixed growth patterns.

In the series by Ryan and Font,[6] none of the exophytic lesions developed into carcinomas, but seven of 12 tumors with either inverted or mixed growth patterns showed foci of carcinoma.

In our Patient 1, there was extensive dysplasia of the papilloma within the lacrimal sac but no evidence of malignancy. Koilocytosis was present within the lacrimal sac tumor, which suggests that this was a viral papilloma. The tumor of Patient 2 showed transformation to an inverted papilloma within the lacrimal sac with no malignant cells seen, but there was no evidence of koilocytosis in any of the pathologic specimens examined.

Both of our patients were initially thought to have medial conjunctival papillomas, but the tumors recurred several times after excision. In each case, recurrences involved the punctum and the lesions extended into the lacrimal sac. Because of the aggressive nature of these lesions, it was necessary to exenterate the lacrimal sac and canaliculi to eradicate the papillomas. One of our patients also had a history of verruca vulgaris, which supports a viral cause of the conjunctival lesions.

Recurrences of conjunctival papillomas after excision are common. Several adjunctive therapies to reduce the incidence of recurrence have been described. Cryotherapy[7] and irradiation with the carbon dioxide laser[8] have both been suggested, but such techniques have not been universally successful in preventing recurrences. We have found cryotherapy applied to −20

C in a double freeze-thaw application to be the most effective technique. Despite treatment with cryotherapy, both of our patients had recurrences, which indicates the virulence of these lesions. Excision with wide surgical margins combined with cryotherapy was necessary to eradicate the tumors. The aggressiveness of these lesions must be recognized before surgical intervention, and careful complete excision of all involved tissue is necessary to reduce the risk of recurrence.

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OPHTHALMIC MINIATURE

As he walked, he was also in the habit of lifting his eyes but not his head to spy out what might just possibly be hiding behind the windows. By the time he got to the end of a street he would feel dizzy from moving his eyes around so much.

Naguib Mafouz, *Palace Walk*
Translated from Arabic by W. M. Hutchins and O. E. Kenny
New York, Doubleday, 1989

Human Papillomavirus Type 18 in Conjunctival Intraepithelial Neoplasia

Simeon A. Lauer, M.D., James S. Malter, M.D., and J. Ralph Meier, M.D.

Human papillomaviruses are oncogenic viruses that have been found in a variety of epithelial neoplasias. We sought to confirm their presence in conjunctival intraepithelial neoplasia. Five tumors were studied with a polymerase chain-reaction assay designed to detect the E6 region of human papillomavirus types 16 and 18. Human papillomavirus type-16 DNA was found in four of the five tumors, including two tumors that contained both type-16 and type-18 DNA. Viral DNA was not present in the fifth tumor.

THE CLINICAL and histopathologic features of nonpigmented conjunctival and corneal epithelial neoplasias were classified by Pizzarello and Jakobiec in 1978.[1] They adopted the nomenclature of anogenital epithelial neoplasias, which have similar histopathologic characteristics. In a conjunctival or corneal intraepithelial neoplasm, dysplastic cells are confined to the epithelium. When these cells have invaded the epithelial basement membrane, the tumor is considered to be a squamous cell carcinoma.

Human papillomaviruses are oncogenic viruses that are present in up to 90% of anogenital epithelial neoplasms.[2] Their presence has recently been demonstrated in conjunctival epithelial neoplasms[3] and in a squamous cell carcinoma of the eyelid.[4] Papillomaviruses induce tumor formation in animals[5] and malignant transformation of cell cultures.[6] The mechanism of oncogenesis is not completely understood.[7]

Human papillomaviruses are divided into types based on homologous characteristics of the DNA sequences.[8] In the anogenital region, types 16[9] and 18[10] have been found predominantly in carcinomas.[11] Thus far, human papillomavirus type 16 is the only type demonstrated in conjunctival epithelial neoplasms.[3] In this study, we confirmed the presence of human papillomavirus DNA in conjunctival intraepithelial neoplasia. Human papillomavirus type 18 was present in two of these tumors.

Material and Methods

Specimens for study were collected from formalin-fixed, paraffin-embedded tissue. The pathologic characteristics were reviewed and the histopathologic diagnosis confirmed for each block by one of us (J.R.M.). Five sections, 10 μm thick, were removed with a clean microtome blade and placed in a microcentrifuge tube under sterile conditions. Paraffin was removed with two xylene extractions, and xylene was removed with 95% ethanol. The tissue was pelleted, residual ethanol was removed, and the specimen was vacuum dried for five minutes before resuspension in 100 μl of water. The specimen was boiled for 20 minutes and the DNA content determined by spectrophotometry. Approximately 2.0 μg of total nucleic acid was used for the polymerase chain-reaction assay.

The polymerase chain-reaction assay was performed in a total volume of 50 μl. Buffer consisted of 17.0 mM of ammonium sulfate, 67.0 mM of Tris-HCl pH 8.5, 10.0 mM of 2-mercaptoethanol, and 170 μg/ml of bovine serum albumin. Magnesium chloride 7.0 mM, a biologic detergent composed of various polyoxyethylene ethers and other surface-active compounds (Triton-X 100, Sigma Chemical Co., St. Louis, Missouri) 0.1%, deoxynucleotides (1.5 mM each), and three units of Taq DNA

polymerase (Promega, Madison, Wisconsin) were added to each reaction mixture. Each specimen was run with type-16 and type-18 oligonucleotide (20 base) primers synthesized according to the sequences reported by Shibata and associates.[12]

Aliquots (1 μg) of DNA extracted from SiHa and HeLa cell culture lines were used as positive controls for human papillomavirus types 16 and 18, respectively. Solutions and primers without DNA served as negative controls.

Amplification consisted of denaturation for one minute at 93 C, annealing for one minute at 47 C, and extension for 30 seconds at 72 C. The amplification process was continued for 35 cycles. Two separate 10-μl aliquots from each of the amplification products were loaded on an ethidium bromide–stained 2% agarose gel, separated by electrophoresis for 45 minutes at 100 V, and transferred to a nylon membrane.

Each amplification product was hybridized independently with human papillomavirus type 16 or 18 oligonucleotide (40 base) probes as described by Shibata and associates.[12] Prehybridization was performed for three hours at 42 C in 50% formamide, five times the standard concentration of sodium chloride, sodium phosphate, ethylene-diaminetetraacetic acid (EDTA) buffer, 0.1% Denhardt's solution, 10 mg/ml of salmon-sperm DNA, and 1% glycine. Hybridization was performed for 24 hours at 42 C in 50% formamide, five times the standard concentration of sodium chloride, sodium phosphate, EDTA buffer, 10 mg/ml of salmon-sperm DNA, and 1% sodium dodecyl sulfate. Membranes were washed with two times the standard concentration of sodium chloride, sodium citrate buffer sequentially at room temperature, 37 C, and 42 C until background radioactivity was undetectable. Autoradiography with Kodak X-AR film and two intensifying screens was performed for three to 12 hours at −70 C.

Results

We studied five conjunctival intraepithelial neoplasms (Table). Representative autoradiograms for three of the tumors showed the presence of type-16 (Fig. 1) and type-18 (Fig. 2) DNA. In Figure 1, the amplified products were hybridized with the human papillomavirus type-16 probe. In Figure 2, the type-18 probe was used for hybridization. Type-16 primers

TABLE

VIRAL DNA IN CONJUNCTIVAL INTRAEPITHELIAL NEOPLASMS

SPECIMEN NO.	HUMAN PAPILLOMAVIRUS DNA	
	TYPE 16	TYPE 18
1	Absent	Absent
2	Present	Present
3	Present	Absent
4	Present	Absent
5	Present	Present

were used for amplification in odd-numbered lanes, and type-18 primers were used in even-numbered lanes.

DNA extracted from the SiHa and HeLa cervical cell lines, which are known to contain human papillomavirus DNA, were used as positive controls. The SiHa DNA, which contains type 16, was used in lane 1. In lane 2, HeLa DNA, which contains type 18, was used. These positive controls yielded a strong single band of the expected size (109 base pairs) as visualized after agarose gel electrophoresis. These amplified fragments hybridized strongly with appropriate probes. A band was not always visible in the agarose gel for the specimens but the autoradiographic bands corresponded precisely with those of the positive control. No DNA was added to the negative controls in lanes 3 and 4. Autoradiography continued to yield negative results even after prolonged exposure.

Amplified DNA from the first specimen was
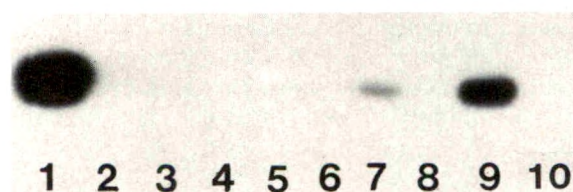
Fig. 1 (Lauer, Malter, and Meier). Southern blot hybridization of polymerase chain reaction product with human papillomavirus type-16 ^{32}P-radiolabeled oligonucleotide probe. Type-16 primers were used in odd-numbered lanes, and type-18 primers were used in even-numbered lanes. The primers were incubated with the following: SiHa DNA (lane 1), HeLa DNA (lane 2), without DNA (lanes 3 and 4), specimen 1 (lanes 5 and 6), specimen 2 (lanes 7 and 8), and specimen 3 (lanes 9 and 10). Lanes 1 (type 16, control), 7, and 9 contain type-16 DNA.
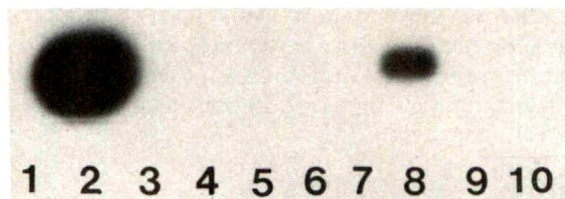
Fig. 2 (Lauer, Malter, and Meier). Southern blot as in Figure 1 hybridized with human papillomavirus type-18 probe. Lanes 2 (type 18, control) and 8 contain type-18 DNA.

subjected to electrophoresis in lanes 5 and 6. No band was visualized with either papillomavirus probe even after prolonged exposure. The amplification product from the second specimen hybridized strongly with the type-18 probe (Fig. 2, lane 8), which showed the presence of human papillomavirus type-18 DNA. A weaker band was also seen with the probe specific for type-16 DNA (Fig. 1, lane 7). The amplification product from the third specimen hybridized strongly with the type-16 probe (Fig. 1, lane 9) but not with the probe for type 18 (Fig. 2, lane 10).

The fourth specimen was strongly positive for human papillomavirus type 16 and did not hybridize with the type-18 probe. The fifth specimen hybridized strongly with both probes.

Discussion

Human papillomaviruses are epitheliotropic oncogenic viruses.[2] They have been found in a variety of epithelial neoplasias, including more than 90% of uterine cervical carcinomas.[2] Human papillomavirus DNA induces malignant transformation of cultured cells in vitro.[6] The ability to transform cultured cells has been traced to the E6 and E7 early open-reading frames of the human papillomavirus genome.[13] The E6-encoded transforming proteins confer tumorigenicity. The E7-encoded proteins confer malignant growth properties. There is evidence that E6- and E7-transforming proteins interact with nuclear proteins.[14] Alternatively, the E6-encoded protein may be a hormone-receptor protein,[15] which is consistent with the hormone dependence of some human papillomavirus–transformed cells.[16]

Human papillomaviruses are divided into types based on homologous characteristics of their DNA sequences.[8] Low-risk types such as 6 and 11 are found in premalignant and benign tumors.[2] These types have been identified in conjunctival papillomas.[17-19] High-risk types such as 16 and 18 are more common in carcinomas.[11]

The E6 region of types 16 and 18 differs from that of other types.[12] The potential for malignant transformation may be linked to the E6* intron, which is unique to these types. Shibata and associates[12] have developed a polymerase chain-reaction assay that is specifically designed to identify the E6 region of human papillomavirus types 16 and 18.

In a polymerase chain-reaction assay (Fig. 3), target DNA is amplified by the enzyme DNA polymerase.[20] This process starts with the denaturation of double-stranded DNA into two single strands. Two oligonucleotide primers hybridize to single-stranded complementary regions of the target DNA. DNA polymerase then extends the primer by using the double-stranded region of the target DNA as a template. The newly synthesized double-stranded DNA is denatured and the cycle repeated. With each cycle, the amount of target DNA is doubled. After 20 to 40 cycles, a small quantity of target DNA can be replicated a billion times.[20] As little as 100 attograms of target DNA can be detected (Pietro Lampertico, M.D., Tulane University College of Medicine, New Orleans, Louisiana, unpublished data) when the assay is coupled with Southern blotting[21] as in this study.

The target DNA is identified by hybridization with a probe. The probe is a radiolabeled oligonucleotide that is complementary to a unique internal region of the amplified target DNA. The presence of bound probes is demonstrated by autoradiography (Figs. 1 and 2).

We used a polymerase chain reaction to demonstrate the presence of human papillomavirus DNA in four of five conjunctival intraepithelial neoplasms. McDonnell, Mayr, and Martin[3] reported finding human papillomavirus type-16 DNA in nine of 13 (69%) conjunctival intraepithelial neoplasms and in three conjunctival squamous cell carcinomas. The two studies combined found human papillomavirus DNA in 13 of 18 (72%) conjunctival intraepithelial neoplasms.

In our study, human papillomavirus type 18 was found in two tumors. Type 16 was found in four tumors including two tumors that contained both types. The significance of finding both types in the same tumor is not known.[22]

We provide evidence for the presence of hu-

Denaturation 93C

Annealing 47C

Extension 72C
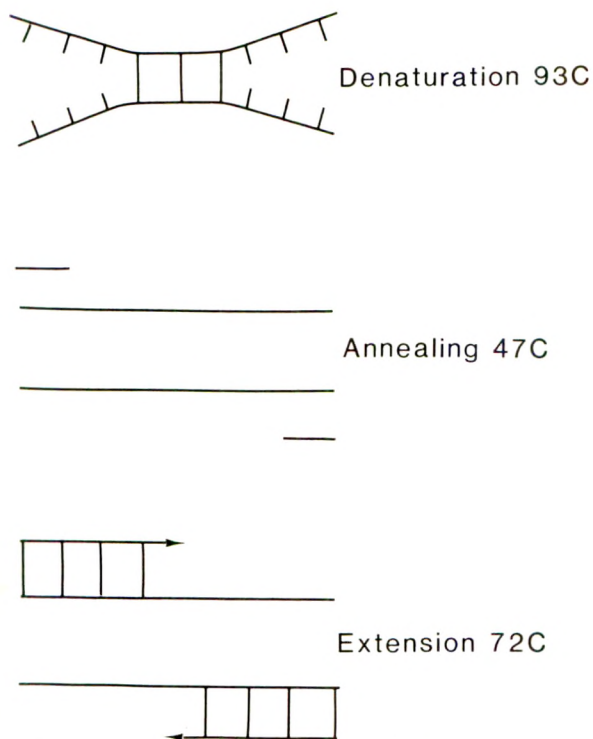
Fig. 3 (Lauer, Malter, and Meier). Schematic diagram of the polymerase chain-reaction sequence. Top, Step 1. Double-stranded target DNA is denatured to single-stranded DNA at 93 C for one minute. Middle, Step 2. Oligonucleotide primers complementary to flanking regions of the target DNA are allowed to anneal at 47 C for one minute. Bottom, Step 3. Primers are extended by the enzyme DNA polymerase by using the single-stranded target DNA as a template.

man papillomavirus type-18 DNA. The band produced by the tumor we studied was identical to that produced by DNA extracted from the type 18–containing HeLa cell line. The assay produced no amplification product when no DNA was added, which confirms that the target DNA was not a contaminant in the reagents. The first tumor did not produce an amplification product, which confirms that the contaminating DNA was not added during processing of the specimens. The third specimen was exclusively positive for human papillomavirus type 16, confirming that cross-hybridization did not occur.

The fifth tumor studied had equally strong bands with both type-16 and -18 probes. This specimen, therefore, contained both types. The weak band that developed (Fig. 1, lane 7) probably represents low-level type-16 infection.

Whether human papillomavirus DNA plays an active role in the development of conjunctival intraepithelial tumors cannot be stated until the mechanism of papillomavirus oncogenesis is better understood.

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OPHTHALMIC MINIATURE

It was an old woman's room, and above the smell of beeswax and the faint summer scent from a bowl of pot-pourri on the Pembroke table, his sensitive nose could detect a whiff of the sour smell of old age. Their eyes met and held. Hers were still remarkable, immense, well spaced and heavily lidded. They must once have been the focus of her beauty, and although they were sunken now, he could still see the glint of intelligence behind them.

P. D. James, *A Taste for Death*
New York, Alfred A. Knopf, 1986, p. 96

Optic Disk Elevation in Down's Syndrome

Robert A. Catalano, M.D., and John W. Simon, M.D.

Of five children who had Down's syndrome with optic nerve head elevation, without associated intracranial lesions, three underwent enhanced computed tomography for which no abnormalities were found. Partial, complete, or intermittent resolution of the optic disk elevation occurred in three children. In none of the children were retinal vessel dilation, splinter hemorrhages, optic nerve drusen, subsequent optic atrophy, or apparent visual loss noted. All of the children were hyperopic, but only one child had a hyperopia of greater than 3.50 diopters.

ALTHOUGH ASSOCIATED ocular abnormalities are frequent, optic nerve abnormalities are rare in Down's syndrome.[1] The only consistent finding has been a hyperemic appearance of the optic disk believed to be secondary to an increased number of vessels crossing the disk margin.[2] Optic nerve hypoplasia has been reported in three patients with Down's syndrome,[3,4] and an optic nerve glioma in one child with Down's syndrome.[5] Down's syndrome has not been associated with optic disk drusen or optic nerve inflammation.

We treated five children with Down's syndrome and optic disk elevation. In all patients the chromosomal abnormality (trisomy 21) was confirmed by karyotyping.

Case Reports

Case 1

A 58-month-old girl was first seen because of an intermittent esotropia. Her medical history

was notable for a sinus venosus atrial septal defect with right atrial and right ventricular hypertrophy and partially anomalous pulmonary venous drainage. Refraction disclosed hyperopia in each eye (spherical equivalent in diopters, +2.50). Both optic nerves appeared elevated with a slight obscuration of the vessels at the disk margin, but without small vessel dilation or retinal hemorrhages (Fig. 1). Using projected Allen pictures, visual acuity in each eye measured 20/40. Results of the neurologic examination were unchanged from previous yearly examinations. Follow-up four months later showed apparent resolution of disk elevation in the right eye and decreased elevation in the left eye. Nine months after the first visit the right optic nerve again appeared elevated and the elevation of the left nerve was more pronounced. At no time were the vessels at the surface of the disk obscured and no splinter hemorrhages or vessel dilation was noted. Over the next 28 months examination results did not

Fig. 1 (Catalano and Simon). Elevated optic nerve head in the left eye of Patient 1. Note the absence of small vessel dilation or hemorrhages, and the preservation of the physiologic cup.
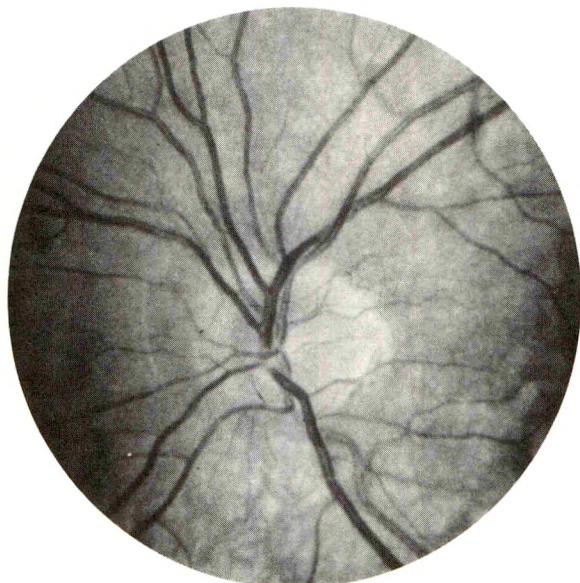
Fig. 2 (Catalano and Simon). Elevated optic nerve head in the left eye of Patient 2. Vessels appear obscured at the disk margin without vessel dilation or hemorrhages.

Fig. 3 (Catalano and Simon). Resolution of optic nerve head swelling in the left eye of Patient 2, 31 months after first examination.

change. No optic nerve drusen or atrophy became apparent.

Case 2

A 42-month-old girl had esotropia and amblyopia of the right eye. A persistent patent ductus arteriosus had been noted on echocardiography, and respiratory arrest had occurred in the neonatal period. Refraction disclosed a moderate hyperopia, greater in the right eye than the left eye (spherical equivalent in diopters, +5.25 in the right eye; +4.50 in the left eye). Both optic disks appeared symmetrically elevated without vessel dilation, hemorrhages, or retinal folds (Fig. 2). Enhanced computed tomography demonstrated no masses or areas of abnormal enhancement. By 73 months of age the patient's refraction had not appreciably changed and no neurologic deficits had developed. The optic nerve head, however, no longer appeared elevated and no optic nerve drusen were evident (Fig. 3). Using projected Allen pictures, visual acuity was R.E.: 20/40 and L.E.: 20/30.

Case 3

A 10-month-old boy had nystagmus and esotropia and amblyopia of the right eye. His

medical history disclosed Hirschsprung disease for which a colostomy was performed at 6 months of age. Cardiac examination at that time, including echocardiography, disclosed no abnormalities. Refraction disclosed hyperopia (spherical equivalent in diopters, +3.50 in the right eye; +3.25 in the left eye). Both optic disks appeared elevated with slight obscuration of the retinal vessels at the disk margins. No vessel dilation or hemorrhages at the disk margin were noted (Fig. 4). Enhanced computed tomography demonstrated no areas of enhancement or evidence of a space-occupying lesion. The patient was examined on 11 occasions during the next 30 months. No engorgement of the retinal vessels or splinter retinal hemorrhages were ever noted. When the patient was 26 months of age partial resolution of the optic disk elevation was first noted, but a slight elevation of both optic nerves has remained. Verbal visual acuity was not attainable, but visual behavior has not deteriorated during follow-up. The amblyopia of the right eye was treated with occlusion therapy and no fixation preference remains.

Case 4

An 11-month-old boy was seen because of nystagmus. A cardiac examination when the patient was 2 months of age had demonstrated no evidence of congenital heart disease. Refrac-

Fig. 4 (Catalano and Simon). Optic disk elevation without vessel dilation or hemorrhages in the left eye of Patient 3.

Fig. 5 (Catalano and Simon). Massive disk elevation without hemorrhages in the right eye of Patient 4.

tion disclosed a minimal hyperopia (spherical equivalent in diopters, 1.75) in each eye. No structural abnormalities of the eyes existed except for bilateral elevated optic nerves. No vessel dilation, splinter hemorrhages, or retinal striae were noted (Fig. 5). Neurologic examination and enhanced computed tomography demonstrated no evidence of a space-occupying lesion. Follow-up over the next 19 months disclosed no change in the appearance of the optic nerves. No apparent visual deficits have developed.

Case 5

An infant girl was noted at birth to have bilateral cortical cataracts. A cardiac examination, including echocardiography, electrocardiography, and chest radiography, performed when the patient was 3 days of age, demonstrated no congenital heart disease. A lensectomy, posterior capsulectomy, and anterior vitrectomy were performed on the left eye at 7 days of age and on the right eye at 14 days of age. Aphakia was corrected in each eye seven days after surgery with a silicone contact lens. Because of nystagmus and an alternating esotropia, first noted at 6 months of age, the patient underwent a recession of both medial recti

muscles at 12 months of age. Examination demonstrated no abnormality of either optic nerve until 24 months of age, at which time the right optic nerve appeared elevated, without evidence of vessel dilation or hemorrhage at the disk margin. Aphakic correction in each eye was spherical equivalent in diopters +18.00. Follow-up six months later showed no change in the appearance of either optic nerve and no fixation preference for the left eye has developed.

Discussion

Computed tomography, performed in three children, disclosed no space-occupying lesions, and no child developed apparent neurologic or visual deficits in follow-up ranging from 6 to 41 months. Partial, complete, or intermittent resolution of the optic disk elevation occurred in three children and the onset of the disk elevation was noted in a fourth child. Disk elevation was unilateral in one child and asymmetric in a second child. In only one child could the onset of the disorder be accurately estimated, but two children were less than 1 year of age when this was first noted. The complete or partial resolution of disk elevation in our two oldest patients suggests that this disorder may remit with age.

The differential diagnosis of optic disk elevation includes papilledema, optic disk drusen, severe hyperopia, optic neuritis, and chronic venous congestion secondary to congenital heart disease. There was no basis for implicating any rare cause of optic disk swelling such as uveitis, hypotony, infiltrative disorders, or orbital tumors in any of our patients.

Elevation of the optic disk is typically a late finding in papilledema. Retinal hemorrhages, exudates, and venous congestion are usually associated with this disorder; other indications of an expanding intracranial mass might also be expected.[6] These findings were absent in our patients.

Drusen embedded beneath the surface of the optic disk are a frequent cause of anomalous disk elevation in children. The elevation associated with disk drusen, however, does not obscure the retinal arterioles lying anterior to it, and the physiologic cup is usually absent. Furthermore, with optic nerve drusen, the most elevated portion of the disk is usually the central area, and the elevated disk often has an irregular border.[6] The elevation of the disk in our patients was more peripheral than central and in three of our patients the physiologic cup was not obscured.

A rare type of disk elevation has been associated with severe degrees of hyperopia. These disk elevations, although lacking true edema, can closely simulate some cases of moderate, subacute papilledema.[6] This optic nerve disorder, however, is usually not progressive and variable resolution and recurrence of optic disk elevation might not be expected. Furthermore, three of our patients had only moderate hyperopia.

Another common cause of optic disk elevation, optic neuritis, is usually associated with at least transient visual loss. There was no evidence of deterioration of vision in any of our patients.

Optic disk elevation has also been described in children with cyanotic congenital heart disease.[7] Mild hypoxia can result in dilated, tortuous retinal vessels, retinal edema, and optic disk edema. These changes can occur in the absence of hypercapnia or increased cerebral spinal fluid pressure. Cyanotic congenital heart disease is usually associated with defects causing shunting of blood from the right to the left side of the circulatory system. None of our patients had transposition of the great vessels, persistent truncus arteriosus, or tetralogy of

Fallot. Two of our patients, however, had conditions that cause left to right shunts. In at least one of these two children right ventricular hypertrophy and pulmonary hypertension had developed, which had the potential for reversal of blood flow, systemic hypoxia, and optic disk edema. Disk elevation secondary to cyanotic congenital heart disease is less tenable in the three patients for whom cardiac examination disclosed no congenital heart disease, but a mild cardiopathy in these children may have been unrecognized.

The cause of the disk elevation in patients with Down's syndrome remains undetermined. Many of the ocular findings in Down's syndrome consist of hyperplasias.[2] All of our patients were hyperopic. It may be that the association of a congenital excess of glia, or some other optic nerve constituent, in association with even a moderate hyperopia or hypoxia can lead to the appearance of optic disk swelling in Down's syndrome. In those patients where the finding was transient or variable an unidentified factor such as ocular hypotony, systemic hypertension, venous congestion, or the patient's cooperation with the examination may have been influential in the degree of optic nerve head elevation noted. The self-correction of an atrial or ventricular septal defect or a patent ductus arteriosus could explain the subsidence of the elevated disk in some children as they mature.

These patients add to the diverse ocular findings in Down's syndrome. The incidence of this finding is difficult to estimate from our referral-based pediatric ophthalmology practices. These five children, however, constitute approximately 5% of the children with Down's syndrome seen in our combined practices. Clinicians should be aware that the optic disk can be elevated in Down's syndrome in the absence of an intracranial mass, disk drusen, or inflammation. This elevation may be transient and recurrent, and it is not associated with apparent visual loss.

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OPHTHALMIC MINIATURE

On the table beside the model were her spectacles—the spectacles that she put on as seldom as possible, owing to vanity, preferring to feel her way almost blindly sometimes, since she admitted to Henrietta that without them she was so short-sighted that she could hardly see a yard in front of her.

Henrietta had nodded comprehendingly. She understood now the physical reason for that blank and lovely stare.

Agatha Christie, *The Hollow*
New York, Berkley Books, 1974, p. 11

Hazards of Laser Beam Reflections in Eyes Containing Gas

Marc M. Whitacre, M.D., and Martin A. Mainster, M.D.

Three patients suffered photic or thermal laser injuries at unintended sites because of reflection from gas-fluid interfaces in eyes containing gas. Fresnel's equations predict the amount of light transmitted or reflected at optical interfaces. Application of Fresnel's equations demonstrate that significant laser reflection occurs at gas-fluid or fluid-gas interfaces, especially at high angles of incidence. Photocoagulation across gas-fluid or fluid-gas interfaces should be avoided to reduce the risk of unintended damage from reflected light. If photocoagulation must be performed across an interface, the surgeon should minimize the angle of incidence of the treatment laser beam, use a divergent beam, and consider the location and intensity of the reflected beam. Because of the higher phototoxicity of blue light, photocoagulation with blue-green lasers across gas-fluid or fluid-gas interfaces is undesirable. Proper polarization of the treatment laser beam may significantly reduce laser reflectance.

INTRAOCULAR GAS is commonly used in the repair of simple or complicated retinal detachments. Laser photocoagulation is often used with intraocular gas for retinopexy of retinal breaks and panretinal photocoagulation. One of us (M.M.W.) has observed that the laser beam is reflected off the gas-fluid or fluid-gas interface in eyes containing gas.

Case Reports

Case 1

A 12-year-old boy with retinopathy of prematurity developed a recurrent rhegmatogenous retinal detachment complicated by intravitreal and epiretinal membranes. He underwent trans pars plana vitrectomy and gas-fluid exchange with retinal cryopexy. Postoperatively the intravitreal gas migrated subretinally because of persistent retinal traction from epiretinal membranes. A trans pars plana lensectomy, membrane peeling, and repeat gas-fluid exchange were performed. The subretinal gas was evacuated and a zone of extensive peripheral retinopexy was created by photocoagulation. A blue-green argon laser indirect ophthalmoscope was used to apply 1,610 lesions with a spot size of approximately 350 μm, an output power of 350 to 700 mW, and an exposure duration of 0.05 to 3.00 seconds. Postoperatively, the patient had severe erythropsia for two days.

Case 2

A 77-year-old man had a retinal detachment from multiple, large retinal tears in the superior and inferior quadrants. He underwent scleral buckling, trans pars plana vitrectomy, retinal cryopexy, and gas-fluid exchange. Postoperatively the patient had a recurrence of a small, inferior retinal detachment associated with a visible retinal hole at the 5 o'clock meridian. Repeat gas-fluid exchange was performed with perfluoropropane. When the gas bubble had expanded to fill the entire vitreous cavity, photocoagulation was applied to the inferior retina. Photocoagulation was performed with 630-nm red laser light using a panfunduscope lens, a beam diameter of 100 μm, and an exposure duration of 0.5 to 3.0 seconds. A total of 350 spots were applied. During photocoagulation it was noted that the treatment laser beam was reflected from the surface of the retina to a

zone slightly inferonasal to the optic disk. The diameter of the reflected beam was approximately 1,500 μm. Several weeks postoperatively the patient had a region of pallor in the area of the fundus struck by the reflected beam, consistent with laser photocoagulation.

Case 3

A 48-year-old woman with proliferative diabetic retinopathy, a tractional retinal detachment, and a chronic vitreous hemorrhage underwent placement of an encircling band, pars plana vitrectomy, membrane peeling, gas-fluid exchange, and endophotocoagulation. Endophotocoagulation of the retina posterior to the apex of the band occasionally resulted in the production of two burns, one at the incident retina on the band and another at a site posterior to the band.

Material and Methods

Light is either reflected or transmitted when it strikes an optical interface. Snell's law relates the directions of incident and transmitted light rays. Fresnel's equations determine the percentage of reflected and transmitted light.[1,2]

For light rays with an electric field polarized perpendicular to the plane of incidence, the reflectance ($R_\perp$, the ratio of the reflected to the incident power) is:

$$R_\perp = \left(\frac{n_i \cos \Theta_i - n_t \cos \Theta_t}{n_i \cos \Theta_i + n_t \cos \Theta_t}\right)^2.$$

In this equation n_i is the index of refraction of the material the incident ray passes through; Θ_i is the angle of incidence; n_t is the index of refraction of the material through which the transmitted ray passes; and Θ_t is the angle of transmission. Both the angle of incidence and the angle of transmission are formed by the light ray and a line perpendicular to the plane of incidence.

The reflectance of light rays with an electric field polarized parallel to the plane of incidence ($R_\parallel$) is:

$$R_\parallel = \left(\frac{n_t \cos \Theta_i - n_i \cos \Theta_t}{n_i \cos \Theta_t + n_t \cos \Theta_i}\right)^2.$$

The reflectance of nonpolarized light is:

$$R_n = \frac{1}{2}(R_\perp + R_\parallel).$$

For light polarized perpendicular to the plane of incidence, the transmittance ($T_\perp$, the ratio of the transmitted to incident power) is:

$$T_\perp = \left(\frac{n_t \cos \Theta_t}{n_i \cos \Theta_i}\right)\left(\frac{2n_i \cos \Theta_i}{n_i \cos \Theta_i + n_t \cos \Theta_t}\right)^2.$$

The transmittance of light polarized parallel to the incident plane ($T_\parallel$) is:

$$T_\parallel = \left(\frac{n_t \cos \Theta_t}{n_i \cos \Theta_i}\right)\left(\frac{2n_i \cos \Theta_i}{n_i \cos \Theta_t + n_t \cos \Theta_i}\right)^2.$$

The transmittance of nonpolarized waves (T_n) is:

$$T_n = \frac{1}{2}(T_\perp + T_\parallel).$$

These equations show that reflectance and transmittance depend not only on the indices of refraction of the incident and transmitting media but also on the angle of incidence and the polarization of the incident light. Reflectances increase and transmittances decrease as the angle of incidence increases. Light with an electrical wave that is perpendicular to the reflecting surface is reflected most; light with an electrical wave parallel to the reflecting surface is reflected least; and unpolarized light waves are reflected an intermediate amount. Passage through a fiberoptic cable depolarizes light, so the laser beams generated by commonly available ophthalmic delivery systems are a form of unpolarized light.

Results

There are four common situations in which reflections off gas-fluid or fluid-gas interfaces occur during photocoagulation. Reflection from a gas-fluid meniscus in an eye of a supine patient is encountered when a laser is directed across a gas-fluid interface at the retina beneath the fluid. If the fluid meniscus is low in the eye high-intensity reflections are unlikely, especially if the laser beam is directed through the pupil (Fig. 1). As the level of the fluid increases the angle of incidence of the laser beam to the fluid level increases, and significant reflections are more probable, especially during endophotocoagulation (Fig. 2).

Reflection from a gas-fluid meniscus in a horizontal eye is commonly encountered during transpupillary photocoagulation with a slit-lamp or indirect ophthalmoscope delivery system. When the fluid meniscus is near the level of the pupil the angle of incidence is high and substantial laser reflections may occur (Fig. 3).
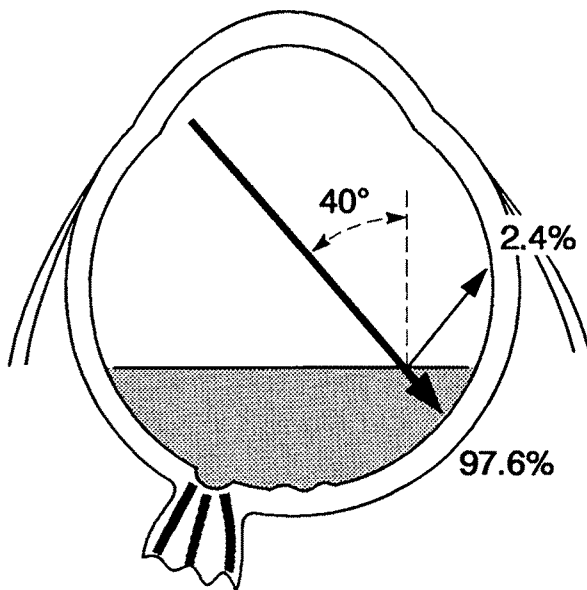
Fig. 1 (Whitacre and Mainster). Laser beam reflection off a gas-fluid meniscus in an eye of a supine patient. If the angle of incidence is 40 degrees, 2.4% of the laser energy incident on the gas-fluid interfaces is reflected.
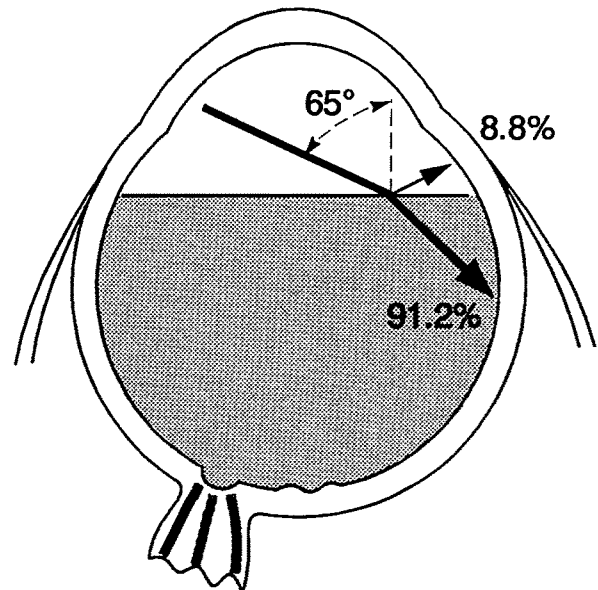
Fig. 2 (Whitacre and Mainster). Laser beam reflection off a gas-fluid meniscus in an eye of a supine patient. If the angle of incidence is 65 degrees, 8.8% of the laser energy incident on the gas-fluid interface is reflected.

Reflection from a fluid-covered structure is encountered in both transpupillary and trans pars plana photocoagulation. Most commonly the reflecting structure is the fluid-covered retina, although reflections could also occur from other structures within the gas-containing portion of the eye, such as ciliary processes or retinal tacks. Directing the beam to the anterior portion of the retina produces a high angle of incidence, especially during endophotocoagulation (Fig. 4). Any distortion of the shape of the eye, as produced by scleral depression or scleral banding or buckling, will decrease the angle of incidence on the anterior portion or apex of the indentation and will increase the angle of incidence posterior to the apex of the indentation (Fig. 5). As described in Case 3, two photocoagulation burns occurred with one discharge of an endophotocoagulation laser when performing photocoagulation on the posterior edge of buckled fluid-coated retina in an eye containing gas.

Reflection from a fluid-gas meniscus is encountered when performing transpupillary slit-lamp or indirect photocoagulation on eyes containing less than a 50% gas fill (Fig. 6). Significant reflection occurs over a narrower range of angles of incidence at fluid-gas than gas-fluid interfaces (Fig. 7). Since high angles

of incidence are needed to visualize anywhere but the most superior portion of the retina covered by the gas bubble, significant laser beam reflection is equally probable at fluid-gas and gas-fluid interfaces. Additionally, there is a critical angle at fluid-gas interfaces at which total internal reflection occurs (48.48 degrees for water-air interfaces). Total internal reflection permits treatment of the retina opposite the gas bubble by using the fluid-gas meniscus as a mirror. One of us (M.M.W.) has performed photocoagulation on retinas opposite the gas bubble in this fashion.

Discussion

Fresnel's equations demonstrate that at a gas-fluid or fluid-gas interface a minimum of 2% of incident unpolarized light is reflected, even at low angles of incidence. This is several times higher than the retinal reflectance at blue-green wavelengths in completely fluid-filled eyes, which varies between 0.12% (419 nm in the fovea) to 0.93% (517 nm in the retinal periphery).[3] Hence, when laser energy is directed through a gas-fluid or fluid-gas interface the interior of the eye is exposed to more reflected
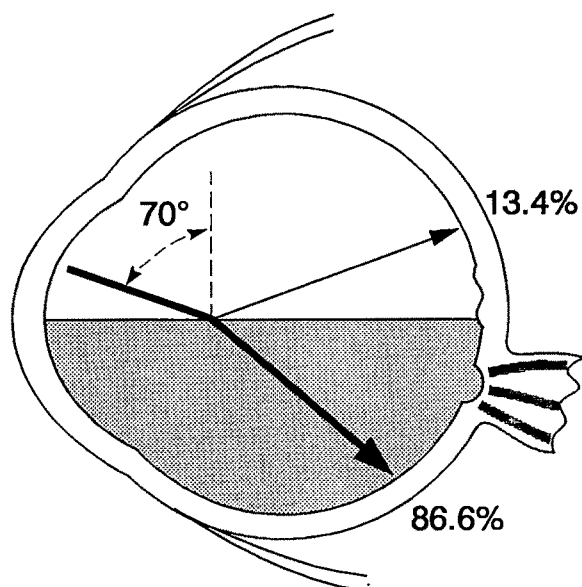
Fig. 3 (Whitacre and Mainster). Laser beam reflection off a gas-fluid meniscus near the level of the pupil in a horizontally directed eye. If the angle of incidence is 70 degrees, 13.4% of the laser energy incident on the gas-fluid interface is reflected.
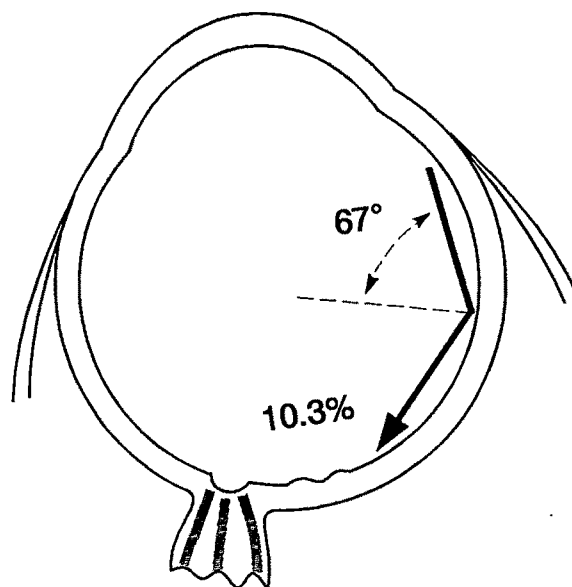
Fig. 4 (Whitacre and Mainster). Laser beam reflection off a fluid-coated structure in a gas-filled eye. A 67-degree angle of incidence on the peripheral retina produces 10.3% reflection of the incident beam.

laser light than would occur if the beam was directed solely through fluid.

At low angles of incidence enough laser energy may be reflected to cause photochemical damage during argon blue-green panretinal photocoagulation.[4-6] This may have occurred in Case 1. At high angles of incidence enough laser power can be reflected off a gas-fluid or fluid-gas interface to cause photochemical damage or even visible thermal burns, regardless of the laser wavelength used. This occurred in Cases 2 and 3.

The risk of unintended photochemical or thermal lesions from laser beam reflection in clinical photocoagulation is higher than expected. This is because eyes containing gas may have a variety of conditions that produce poor transmission or uptake of the laser beam. A cataract or mild vitreous hemorrhage may interfere with the transmission of the laser beam. The gas-fluid or fluid-gas interface may defocus the incident beam, reducing its power density. Subretinal fluid may interfere with uptake of the laser energy. At high angles of incidence the power density of the beam incident on the target tissue decreases because the beam is dispersed over a larger area. Therefore, high power levels or long-duration burns are commonly needed to produce adequate photocoag-

ulation in eyes containing gas. As the angle of incidence on a gas-fluid or fluid-gas interface increases, the surgeon may observe a decreased laser effect on the retina. Believing this to be caused by a media opacity, beam defocusing, or subretinal fluid, the surgeon may increase the already high laser output power. This will further increase the intensity of the reflected beam and significantly increase the patient's risk of unintended phototoxic or thermal injuries.

A variety of factors may prevent immediate or late recognition of unintended laser damage. Because the view of the fundus is not clear in many eyes containing gas, the production of thermal burns may not be recognized. The limited field of view of the fundus obtained by the surgeon may not show the site struck by the reflected beam. Even if the surgeon carefully monitors the site contacted by the reflected beam, a phototoxic or thermal injury can still occur. Extensive preexisting abnormalities and expected postoperative changes may hamper postoperative recognition of unintended thermal or photochemical effects.

Because of the hazards associated with beam reflections, photocoagulation through gas-fluid and fluid-gas interfaces should be minimized. Positioning of the patient's head or eye sometimes allows photocoagulation through the
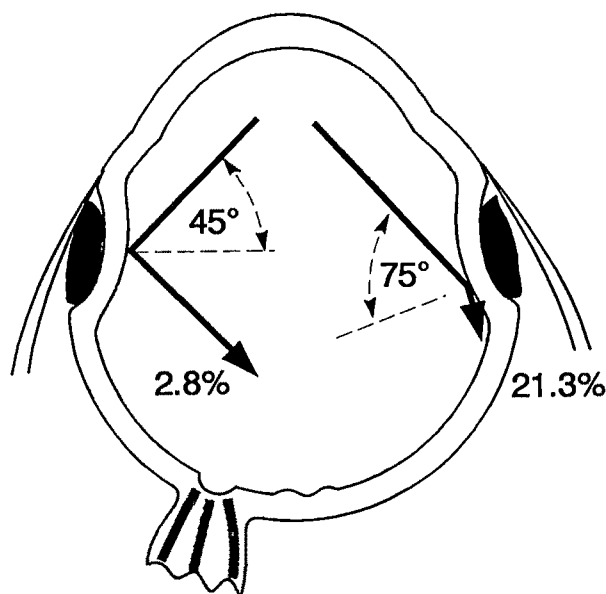
Fig. 5 (Whitacre and Mainster). The effect of indentation on laser beam reflection off a fluid-coated structure in a gas-filled eye. On the apex of the indentation the angle of incidence is 45 degrees, which produces 2.8% reflection. On the posterior slope of the indentation the angle of incidence is 75 degrees, and 21.3% reflection results.
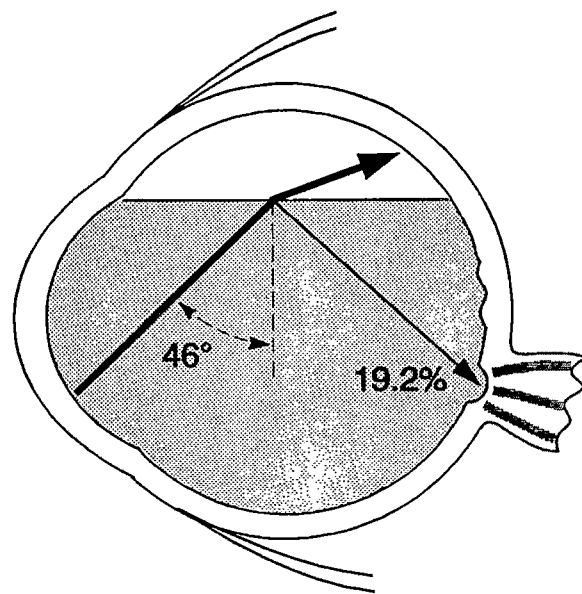
Fig. 6 (Whitacre and Mainster). Laser beam reflection off a fluid-gas meniscus. At an angle of incidence of 46 degrees, 19.2% of the incident energy is reflected.

fluid-filled portion of the vitreous cavity, avoiding beam reflection from gas-fluid or fluid-gas interfaces. If photocoagulation through an interface is necessary, reflectance should be minimized using as low an angle of incidence as possible (keeping the laser beam as perpendicular as possible to the gas-fluid interface). If an

endophotocoagulator is being used, this can sometimes be accomplished by moving the endophotocoagulator probe from one sclerotomy to another or using an endophotocoagulator probe with a bent tip. If an indirect photocoagulator is used, the angle of incidence of the beam on the peripheral retina can be modified by scleral depression. If a slit-lamp photocoagulator is used, a spot size should be selected that produces greatest laser beam divergence in the reflected beam yet still provides sufficient power density to photocoagulate the target tis-
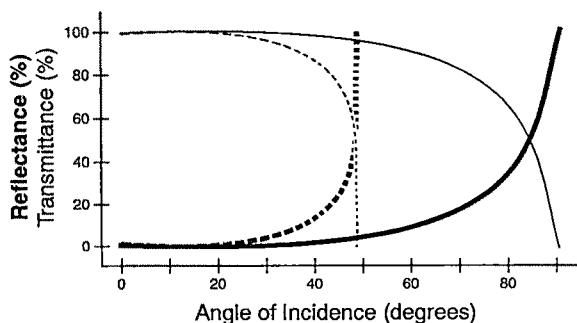
Fig. 7 (Whitacre and Mainster). The relationship between the angle of incidence (Θ_i), reflectance, and transmittance for unpolarized light at air-water and water-air interfaces. Reflectance at a fluid-gas interface (thick broken line); transmittance at a fluid-gas interface (thin broken line); reflectance at a gas-fluid interface (thick solid line); transmittance at a gas-fluid interface (thin solid line).
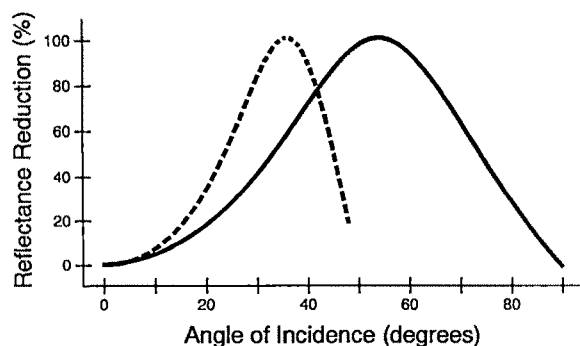
Fig. 8 (Whitacre and Mainster). The percent reduction in reflectance achieved by using parallel-polarized laser energy instead of unpolarized laser energy at water-air (dotted line) and air-water (solid line) interfaces at varying angles of incidence.

sue. The location of the reflected beam should be ascertained before a burn is placed to avoid inadvertent exposure of the optic nerve or macula to the laser energy. When the intensity of a retinal burn decreases, the surgeon should observe if the change in the retinal effect was coincident with a high or increasing angle of incidence of the laser beam on a gas-fluid or fluid-gas interface. If a high angle of incidence is judged to be responsible for the decreasing intensity of retinal burns, careful consideration should be given before proceeding with additional photocoagulation. Because of the greater toxicity of shorter wavelength light it would appear prudent to avoid using 488-nm argon blue for photocoagulation across gas-fluid or fluid-gas interfaces.

The safety of photocoagulation in eyes containing gas could be enhanced by performing photocoagulation with linearly polarized laser energy and adjusting the angle of polarization to minimize the reflection across the gas-fluid or fluid-gas interfaces (Fig. 8). For any angle of incidence, light polarized parallel to the interface is reflected less than unpolarized light or light polarized perpendicular to the plane of incidence. Indeed, at Brewster's angle ($\Theta = \tan^{-1} [n_2/n_1]$) none of the light polarized parallel to the incident plane is reflected. If parallel polarized light is used, reflected laser energy can be reduced by 50% or more over a large range of angles of incidence.

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Eye Shield for Patients Undergoing Laser Treatment

Christine C. Nelson, M.D., Krystyna A. Pasyk, M.D., and Gregory L. Dootz

We developed a patient eye shield consisting of a sandwich of polymethylmethacrylate and tinfoil to provide corneal and retinal protection from inadvertent injury during argon, neodymium:YAG, or dye laser treatment. The shield was tested with argon, dye, neodymium:YAG, and CO_2 lasers. This new eye shield is safe, comfortable, and easy to clean and use.

LASER TREATMENT of vascular and nonvascular skin lesions on and around the eyelids is considered the domain of several specialties, including ophthalmology, dermatology, plastic surgery, otolaryngology, and oncology. Surgeons wear protective eye goggles during laser treatments, and the patient may wear similar goggles if the area of treatment is distant from the ocular adnexa. Eye shields, however, are needed during laser treatment of eyelids and periorbital lesions.[1,2] The risk of inadvertent injury to the patient's eye as well as to the eyes of the surgeon and the operating room personnel is significant if proper protective measures are not taken. The lens of the eye may focus the laser light dangerously by concentrating the energy directly on the retina, thus causing thermal or photochemical damage or both. Because there is typically no pain or discomfort associated with retinal laser burns, the damage that the burns cause will only be found during an ophthalmic examination in which the patient's pupils are dilated.

Eye shields commonly used in eyelid and orbital surgery have been inappropriately used during treatment with lasers. Such use is dangerous because protective plastic devices used for eyelid surgery either absorb or transmit laser light, thereby generating heat or allowing retinal damage.[3,4] The metallic devices are thick and heavy, which causes discomfort and distortion of the eyelids. Additionally, because of the devices' highly polished surfaces, specular reflection can occur. Therefore, a new prototype is necessary to protect the eyes of the patients and operating room personnel. Patient comfort and physician acceptance are as important to eye protection as is proper wavelength filtration. We developed a patient laser eye shield that decreases the risk of specular reflection and is safe, easy to use, and comfortable for the patient.

Material and Methods

The eye shield is made of alternating layers of clear polymethylmethacrylate and tinfoil. The prototype consists of the following layers: 0.5 mm of polymethylmethacrylate, two 0.02-mm layers of tinfoil, 1 mm of polymethylmethacrylate, another layer of 0.02 mm of tinfoil, and a 0.5-mm posterior coating of polymethylmethacrylate (Fig. 1). The anterior surface of polymethylmethacrylate varies in thickness in the area of the 1-cm handle. The eye shield measures 2.8 × 2.5 cm and weighs 3.0 g.

The eye shield should be sterilized before surgical use. The laser shield must be sterilized with gas or soaked in 10% formaldehyde solution for 20 minutes and thoroughly rinsed with sterile water. Alcohol must not be used on the laser shield because it will damage the polymethylmethacrylate coating. Before inserting the shield, a small amount of lubricating ophthalmic ointment is applied to the posterior concave surface of the sterile eye shield.

Before insertion of the eye shield, the patient's eyes should be anesthetized with one to two drops of topical ophthalmic anesthetic solution. Eye shields should be placed in both eyes to ensure adequate protection to the eye not undergoing laser treatment. Placement of
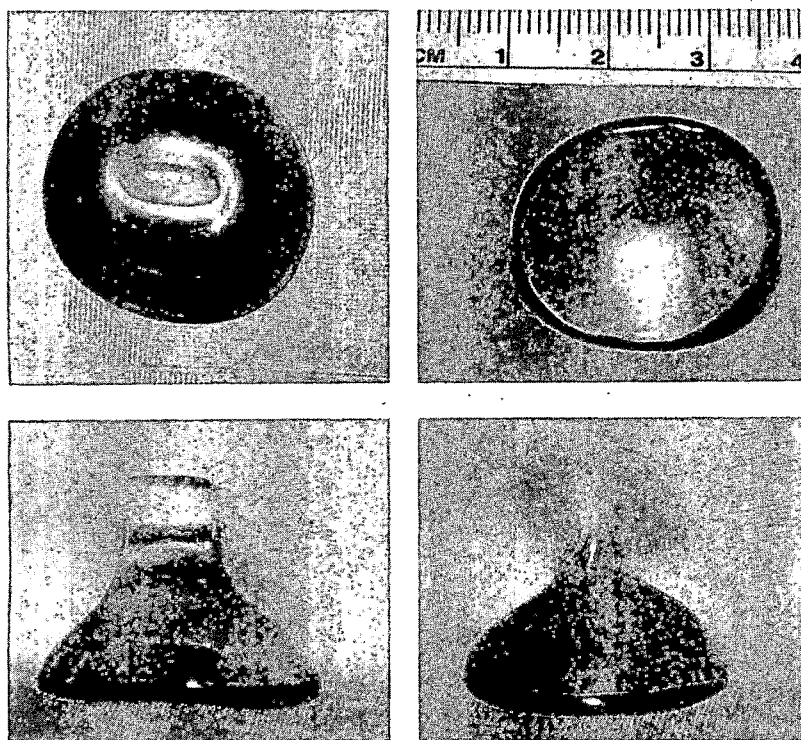
Fig. 1 (Nelson, Pasyk, and Dootz). Patient laser eye shield. Top left, Anterior convex surface. Top right, Posterior concave surface. Bottom left, Note small polymethylmethacrylate handle. Bottom right, Side view of eye shield.

the eye shield may be accomplished with either forceps or fingers. The polymethylmethacrylate handle allows easy insertion and removal of the shield (Fig. 2). The eye may be rinsed after removal of the shield if any ointment remains.

The prototype eye shield was tested for its effectiveness and limitations by the Chemistry and Materials Science Laser Spectroscopy Laboratory at our institution. In this laboratory, two kinds of lasers were used: the argon laser (488 to 514 nm) Coherent CR 18 model (Coherent Medical Company, Palo Alto, California), and neodymium:YAG laser (1,064 nm) Quantronix 416 model (Quantronix Corporation, Smithtown, New York). The laser beam was directed perpendicular (normal) to the plane formed by the posterior outer circular edge of the shield. The power of the argon laser was increased from 0.5 to 3.5 W with a beam diameter of 2 mm in continuous-wave mode. The exposure time varied from ten seconds to ten minutes. The power of the Nd:YAG laser was gradually increased from 1 to 9 W with a beam diameter of 1 mm in continuous-wave mode. The exposure time varied from three seconds to five minutes.

Before clinical studies, the prototype eye shield was tested with three clinical lasers: the argon laser (Meditec DL 5000 dermatologic

model, Aesculap, Burlingame, California); the tunable dye laser (Meditec MDS-10 type, Aesculap); and the CO_2 laser Coherent Medical Group Xanar (Coherent Medical Company, Palo Alto, California). The argon laser power was varied from 2 to 4 W by using a 1-mm spot size in continuous-wave mode from one second to one minute. The dye laser was tested at three wavelengths (577, 600, and 630 nm) from one to ten seconds while the power remained at 1 W in continuous-wave mode with a 1-mm spot size. The CO_2 laser was tested from one second to one minute of exposure time with powers varying from 0.5 to 10 W using the unfocused mode. In the focused mode, the CO_2 was tested with 0.1-mm and 0.2-mm spot size from one to five seconds of exposure time. After each laser testing, the eye shield was examined for thermal damage, perforation, and any increase in temperature to palpation on the posterior surface.

Results

With the Coherent CR 18 argon laser, there was no effect on the eye shield with a 2-mm beam in continuous mode with 1 W of power for

Fig. 2 (Nelson, Pasyk, and Dootz). Laser eye shield on patient with no interference of eyelid position.

one minute. There was a slightly warm area on the anterior surface of the shield but no residual dimple or burn with an increase in the power to 2 W for five minutes. Similarly, the anterior surface warmed slightly but there was no damage after 15 seconds of exposure to the argon laser at 3 W.

With the Quantronix 416 model Nd:YAG laser, no effect on the eye shield was noted with a 1-mm beam diameter in continuous-wave mode at 1 W of power for five minutes. Increasing the power to 3 W for 30 seconds caused the anterior surface to become warm. A small white outward protrusion formed on the anterior surface of the eye shield after a five-second exposure of the Nd:YAG laser beam at 5 W of power. This shield was perforated with 9 W of power after ten seconds of exposure to the 1-mm beam size in continuous-wave mode.

With the clinical Meditec DL 5000 dermatologic model argon laser, no reaction on the eye shield was observed after a 15-second exposure to 3 W of power with a 2-mm spot size in continuous-wave mode. The shield was perforated after 30 seconds using a 1-mm spot size at a power of 4 W in continuous-wave mode.

With the Meditec MDS-10 type Dye Laser, the eye shield was not affected by a power of 1 W with a 1-mm spot size in continuous-wave mode for 10 seconds at 577 nm, 600 nm, or 630 nm.

With the CO_2 laser Coherent Medical Group Xanar, there was no effect on the eye shield with 0.5 W of power unfocused for one minute. As the power of the unfocused beam was increased to 4 W, the anterior polymethylmethacrylate surface became warm and eventually melted. No perforation of the shield, however, was noted after one minute of exposure time. Using a focused 0.2-mm beam of the CO_2 laser for five seconds at 2 to 5 W, the anterior surface became warm and gradually melted. However, there was still no perforation. The shield was perforated after one second with 10 W of power with the CO_2 laser.

Discussion

With increased use of lasers by a variety of specialists, there have been more reports of injuries, making safety standards important.[5-9] The Laser Institute of America provides guidance for the safe use of lasers and laser systems.[10,11] Detailed guidelines and improved goggles were developed to protect the eyes of those who work with lasers. The goggles are used to avoid damage from stray, reflected light and sometimes even direct laser light. For increased protection, both surgeon and patient wear similar safety goggles during laser therapy if the area of treatment is distant from the eyelids. Little has been written, however, about protecting the patient when the standard safety goggles are inappropriate, for example, when they are too large for a child or if the eyelid and orbital areas are to be treated. No matter how effective the protective eyewear, it will be practically useless if it is so uncomfortable for the patient, or so difficult for the surgeon to use, that it is used reluctantly or not at all.

The Smith Evaginated Corneal Protection Shield (Mager and Gougelman, New York, New York) was originally developed to protect the patient's eye from the surgeon's scalpel. These shields have been used during periorbital laser surgery.[4] The green color of this shield absorbs the laser light. The absorbed laser energy is subsequently converted to heat and may cause damage to the polymethylmethacrylate and consequently the eye itself.

The Hornblass Ocular Protection Shield (Mager and Gougelman, New York, New York), also made of polymethylmethacrylate, has also been reported for use with lasers.[1,4] The intended use of this shield was to protect the eye from

Fig. 3 (Nelson, Pasyk, and Dootz). Stefanovsky device sinks into inferior fornix because of the device's weight. Handle interferes with laser treatment of lower eyelid (arrow).

the scalpel during surgery; it was never intended to shield the patient from the laser. Furthermore, because they are produced in a variety of colors, the Hornblass shield absorbs laser energy in the same detrimental manner as does the Smith Shield.

The Stefanovsky Laser Protective Eye Shield (Stefanovsky and Associates, Willowick, Ohio), however, was developed specifically for use with the laser. It is made of high-grade, highly polished stainless steel, which makes it virtually impenetrable to the laser beam. Unfortunately, it also has disadvantages. This eye shield subjects operating room personnel to the risk of specular reflection during laser use. The risk is so high that the Stefanovsky shield comes with this warning. Additionally, because it is heavy and thick, it is uncomfortable for the patient. Further, the knurled ball-grip feature, although it allows effortless placement and removal, extends 1.3 by 0.6 cm, and therefore often interferes with laser surgery directed at the eyelid margin or pretarsal eyelid area. Moreover, because this eye shield is heavy (weight, 9.9 g), it sinks slowly into the inferior fornix during laser treatment (Fig. 3). This disadvantage requires the surgeon to hold the grip throughout the laser treatment to allow proper protection of the globe and to allow the lower eyelid to be treated. The manufacturer does not recommend this shield for use with the Nd:YAG laser.

The new patient laser eye shield has been developed to protect the patients' eyes during treatments to the ocular adnexa. All physicians currently using the argon, dye, or Nd:YAG lasers as well as the CO_2 laser at low power would be able to use the shield to protect their patients' eyes. Our new patient eye shield is sturdy and resistant to heat buildup and specular reflection. The clear polymethylmethacrylate allows the laser light to be diffusely reflected off the dull tinfoil layer rather than be absorbed. There is, therefore, no heat damage to the polymethylmethacrylate and no harmful specular reflection.

The new eye shield has been tested to withstand the direct argon laser light in continuous-wave mode with a 1-mm spot size for 15 seconds of exposure at a power of 4 W. Typically, the power of the argon laser used in the treatment of the eyelid area is between 1.0 and 1.7 W, so the shield would be safe for clinical needs. It has been found to be safe with the Nd:YAG laser in continuous-wave mode using a 1-mm spot size at a power of 2 W for five minutes of exposure. It can also be safely used with the dye laser (577 nm, 600 nm, and 630 nm) at a power of 1 W and a 1-mm spot size in continuous-wave mode. At these settings, the shield would protect the globe from any heat or light energy injury.

The eye shield is also effective in protecting the globe from the CO_2 laser at low power (0.5 W) in focused and unfocused modes and at higher powers up to 5 W in focused and unfocused modes for brief (five seconds or less) exposure times. Moreover, this laser eye shield may be used safely in the operating room to protect the globe from scalpel injury during routine eyelid surgery. Any physician using an argon, dye, Nd:YAG laser, or CO_2 laser on the face, especially around the eyes, wants safety and comfort for the patient as well as ease and flexibility during the treatment. The new laser shield is safer, more comfortable, and more flexible than any being currently used.

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OPHTHALMIC MINIATURE

So through the eyes love attains the heart:
For the eyes are the scouts of the heart,
And the eyes go reconnoitering
For what it would please the heart to possess.
    Guiraut de Borneilh (1138-1200?)

Joseph Campbell (ed.), *The Power of Myth*
New York, Doubleday, 1988, p. 186

Irradiation of Malignant Eyelid Melanoma With Iodine 125 Plaque

Alexander Stanowsky, M.D., Hauke F. Krey, M.D., Jürgen Kopp, Ph.D.,
Werner Kanitz, M.D., and Theodor Wagner, M.D.

We used contact irradiation with iodine 125 seeds to treat a large, exulcerative, nodular, amelanotic malignant eyelid melanoma with metastasis to the regional lymph nodes in an 80-year-old man. The procedure was similar to iodine 125 plaque irradiation of malignant choroidal melanoma; special equipment, however, was needed to protect the eye from radiation exposure. The response of the malignant eyelid melanoma to iodine 125 plaque irradiation was similar to that of malignant melanomas of the choroid. No complications were observed in a follow-up period of 15 months.

Malignant eyelid melanoma can be treated by surgical excision, cryocoagulation, chemotherapy, or irradiation. Most investigators favor complete surgical excision extending as far as possible into healthy tissue, with or without primary or secondary grafting, Mohs' fixation, or fresh tissue techniques.[1-6] It is clear, however, that the safety margin of 2 to 5 cm of healthy tissue normally recommended for dermatologic extirpation[7] would be equivalent to orbital exenteration, and therefore is obsolete if there is any possibility to preserve organ functionality. Cryosurgery[8-11] is best suited for treatment of eyelid tumors that have an invasion depth of up to 0.75 mm.[12] Chemotherapy should be viewed as an adjuvant therapy or a last resort for extensive, inoperable eyelid melanomas.[13]

Lederman, Wybar, and Busby's[14] investigation of radiotherapy for malignant ocular melanoma is extensive. Their study of 184 patients over a period of 40 years disclosed that malignant eyelid melanomas, in contrast to those of the conjunctiva, are mostly resistant to conventional radiation treatment and thus behave like other cutaneous melanomas. In contrast, contact irradiation (especially radioactive plaques containing cobalt 60,[15] ruthenium 106,[16] or the recently favored iodine 125[17]) of malignant choroidal melanomas has proved to be effective. Because of the previous encouraging results with iodine 125 irradiation of malignant choroidal melanomas,[18] we used it in the contact treatment of a large cutaneous eyelid melanoma.

Case Report

A 77-year-old man came to our eye clinic in September 1984 for a planned bilateral cataract extraction. At that time, a 1-mm, pain-free induration was situated near the middle of the right upper eyelid margin. It was diagnosed as a scar from a previous, spontaneously healing hordeolum, and phacoemulsification (with posterior chamber lens implant) was performed in the left eye, and later in the right eye. The patient was again examined in April 1986. The induration of the right upper eyelid had become a 5-mm, immobile, pain-free, nonpigmented growth without accompanying inflammation. A biopsy specimen was taken with local anesthesia from the apparently tumorous area. Histologic examination confirmed a fibroma with no indication of a malignant tumor or an inflammatory process.

At a re-examination in March 1987, we were informed by the referring physician that a biopsy specimen after an operation for presumed chalazion had confirmed an amelanotic malignant melanoma (Fig. 1). Clinical examination at this time disclosed a solid, nonpigmented, firm, pain-free tumor 20 mm in length, 12 mm in
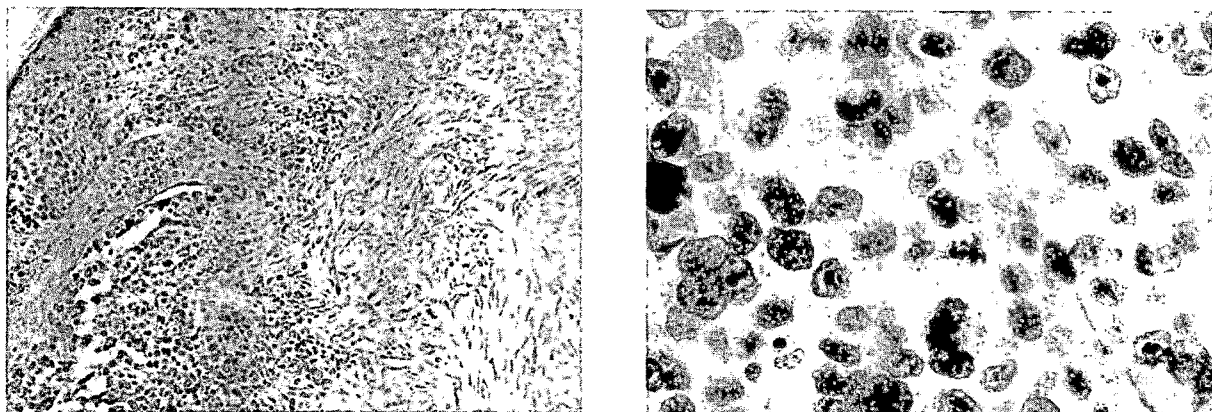
Fig. 1 (Stanowsky and associates). Biopsy material showing invasive amelanotic malignant cutaneous melanoma of the eyelid. Nested accumulations of atypical epithelioid melanocytes in the corium and intraepithelially. Infiltration exceeds 1.5 mm. Clark level IV, pT 3 (minimal). Immunohistologic staining showed protein S 100 in the tumor cells (left, hematoxylin and eosin, × 125; right, × 600).

width, and 7 mm in apex height. The tumor margins were slightly inflamed, and the tumor surface was knobby. There was also a pea-sized, firm, pain-free induration in the medial lower eyelid. The enlarged right preauricular lymph node cluster was 1 cm in diameter, mobile, and pain-free. Bone scintigraphy showed an increased concentration of technetium 99m Methylene-Di-Phosphonate throughout the upper eyelid, the os lacrimale, and the medial lower eyelid, with a possible increase in the right preauricular lymph node cluster. Cranial computed tomography and ear, nose, and throat, internal, urologic, and dermatologic examinations yielded no evidence of additional tumor. The tumor was classified as a nodular malignant melanoma with a thickness of more than 4 mm (pT4), with satellite formation and regional lymph node metastasis (N2).

The patient rejected therapy at first. In June 1987, the upper eyelid tumor developed ulceration with spontaneous hemorrhaging and increasing discomfort.

The patient continued to reject surgical intervention and chemotherapy. He agreed, however, to radiotherapy under the condition that damage to the eye would be avoided as far as possible. He rejected a radiation treatment of the preauricular lymph node cluster.

Material and Methods

The iodine 125 radiotherapy consisted of a radiation applicator (containing iodine 125 seeds) and a radiation shield. Therapy was started in July 1987.

The radiation applicator was made of hardened, transparent, plastic polymethylmethacrylate. After the eyebrows had been coated with Vaseline, a silicone impression mass was pressed onto the closed eyelids. The impression was then filled with plaster, and the resulting cast was used to make a form-fitting applicator that extended 1 cm beyond the bony orbital wall. The tumor perimeter was outlined on the transparent applicator. Depressions were hollowed out within this area at predetermined locations. Iodine 125 seeds were glued into the depressions with fast-drying glue and covered with polymethylmethacrylate. The finished applicator was fixed in place with adhesive strips attached to the patient's face.

The radiation shield was made of gold (Fig. 2) with a maximal thickness of 1.5 mm and was designed for placement in the conjunctival sac to protect the patient's eye. After drop anesthesia of the conjunctiva (proparacaine hydrochloride) and retraction of the eyelids with an eyelid retractor, the conjunctival sac was completely filled with impression material. An impression spoon with notched edges was pressed onto the material and removed with it after five minutes of hardening. After plaster casting of this impression, a disk-shaped 0.1-mm-thick piece of plastic film, 16 mm in diameter, was placed on the cornea of the plaster model to prevent direct contact later between the shield and patient's cornea. The film and the conjunctival sac of the plaster model were then covered with a wax layer that varied from 1 mm in
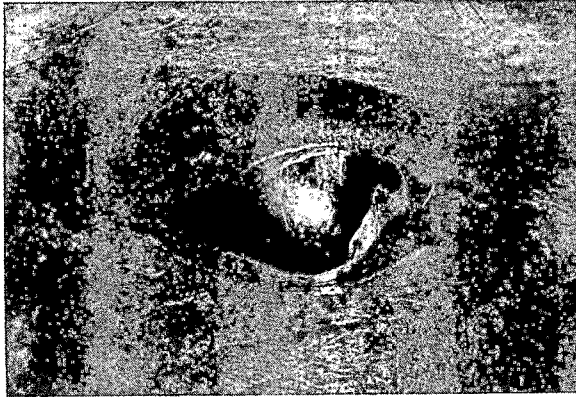
Fig. 2 (Stanowsky and associates). Eyelid melanoma before irradiation with radiation shield in place.

thickness to 1.5 mm near the superotemporal conjunctival fold. The radiation shield itself was prepared from this wax casting the same way as a dentist prepares a dental crown.

A 1:1 scale drawing of the tumor was prepared, based on clinical measurement of the tumor's length and width and ultrasonographic determination of its apex height.[19] The positions of the iodine 125 seeds were included in the drawing. The dose delivered was calculated with the following formula:

$D = T \times G(r) \times \Gamma \times \Sigma_i (A_i \times r_i^{-2})$
T = plaque exposure time (h)
$G(r)$ = radial dose function ($\approx$ 1 for r < 1 cm)
Γ = specific gamma constant (12.7 mGy $\times$ cm^2 $\times$ h^{-1} $\times$ mCi^{-1})
Σ = mathematical sum over i-seeds
A_i = activity of the i-th seed (mCi)
r_i = distance of the i-th seed to the point for which the dose is to be calculated (cm)

The dose had to be calculated at the most distant point irradiated. For our patient, this point was located on the inner eyelid surface in the area of maximum sagittal tumor prominence. The distance between the geometric center of the radiation source and the anterior eyelid surface was 2 mm.

The radiation shield was positioned in the conjunctival sac, and treatment with the applicator was started. The coordinates and activities of the five seeds affixed to the applicator are given in Table 1.

The dressing was changed daily after slit-lamp examination, applanation tonometry, and the application of antibiotics (gentamicin sulfate), corticosteroids (dexamethasone), and 2% atropine ointment in the conjunctival sac. Radi-

TABLE 1
IRRADIATION PARAMETERS (DOSE, 118 Gy)

SEED NO.	COORDINATES (CM)		ACTIVITY, MCi	IRRADIATION FOCUS (CM)		
	X	Y		X	Y	Z*
1	0	0.7	14	0	0	0.7
2	1.4	0	14			
3	0.5	−0.5	14			
4	−0.5	−0.5	14			
5	−1.4	0	14			

*Distance from seed-plane to distal apex of the tumor, expressed as a coordinate.

otherapy was terminated after 172.6 consecutive hours.

The dose rate in the irradiated area was calculated as 0.7 Gy/hour with a total irradiation dose of 118 Gy. The isodose distribution along a plane of frontal section through the tumor's center of irradiation is shown in Figure 3. The radiation dose on the anterior eyelid surface amounted to about 250 Gy. The lacrimal sac received approximately 60 Gy.

Results

The patient died in October 1988 from complications of a bronchial carcinoma. An autopsy was not performed. The follow-up period after radiotherapy was 15 months. There was reddening and swelling of the eyelid during the first three weeks after irradiation, which regressed completely by the 12th week. Scarring was visible after the 15th posttreatment week, but no impairment of function attributable to eyelid shrinkage was observed. Epilation of eyebrows and eyelashes occurred in the irradiated area after the second posttreatment month. No leukoplakia was seen. The lacrimal drainage system remained unobstructed, and reflex and basal tear production remained normal. Visual acuity of the right eye improved from 20/60 to 20/28 because of tumor regression and freeing of the optic axis.

Angiography in March 1988 showed normal iris vessels in the right eye, with no indication of rubeosis or hyperemia.

Before radiation treatment, the upper eyelid tumor measured 42 (length) × 25 (width) mm, with a sagittal apex height of 9 mm; these
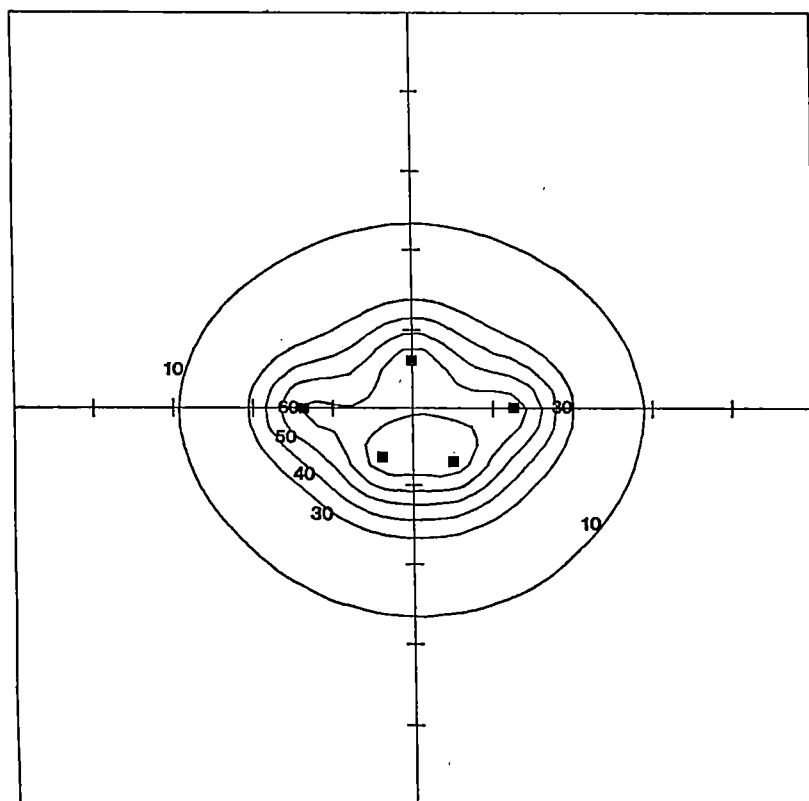
Fig. 3 (Stanowsky and associates). Isodose distribution over a frontal sectional plane through the tumor at the point of greatest prominence.

measurements regressed to 35, 20, and 7 mm, respectively, by the end of irradiation. After 14 months the residual element in the temporal upper eyelid was approximately 8 mm both in length and width and 2 mm in apex height. The residual element can be assumed to have been connective tissue. Other dates of regression are shown in Table 2.

In contrast, the clinically presumed metastasis to the right preauricular lymph node cluster grew steadily. Immunoscintigraphy (melanoma-specific antibody HMW-MAA 225.28S marked

with technetium 99m) showed a specific concentration in this area.

Discussion

The tumor regressed almost completely after irradiation with the iodine 125 applicator. There were no noteworthy complications during the 15 months of follow-up. The metastasis present before irradiation near the right preauricular lymph node cluster, however, grew continuously during the same period.

The rate of regression of the irradiated eyelid melanoma is comparable to that seen after radiotherapy of malignant choroidal melanoma with an iodine-125 applicator.[18] We believe that radiotherapy of malignant melanoma of the skin can be as effective as that of the choroid. The application of radiotherapy, however, must be continuous and long-term. The dose rate being low, total dose must be sufficiently high because of the differences in biologic effectiveness in the kinds of radiation applied.[20] We consider it justified to use similar applicator techniques for inoperable malignant melanomas of the integument located elsewhere.

TABLE 2
REGRESSION OF EYELID MELANOMA AFTER IRRADIATION

| | DIMENSIONS OF UPPER EYELID TUMOR (MM) | | | | | | | |
| | PREOP-ERATIVE | POSTOPERATIVE (MOS) | | | | | | |
		1	2	4	6	8	10	12	14
Depth	9	7	6	5	5	4	3	3	2
Length	42	26	20	19	18	15	11	9	8
Width	25	16	14	13	12	11	9	8	7

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Simultaneous Bilateral Diffuse Melanocytic Uveal Hyperplasia

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Klaus-Peter Steuhl, M.D., and Hans-Jürgen Thiel, M.D.

A 52-year-old woman noted loss of vision in August 1984. Clinical examination disclosed iris cysts and ciliary body cysts, macular edema, and uveal nevi. Cataract extraction and pressure-lowering operations were required in both eyes because of a tumor-induced angle-closure glaucoma. Vision, however, progressively decreased to light perception in each eye. Both eyes were finally enucleated because a malignant melanoma could not be ruled out, though iris tissue obtained in 1985 suggested a nevuslike process. Histologic study indicated a bilateral uveal hyperplasia. Results of light and electron microscopy, immunologic studies, and suspension cell culture suggested that the uveal hyperplasia was more likely a melanoma of low malignancy than a nevuslike process. We could not detect an extraocular primary tumor and assumed that this condition constituted an oncogenic syndrome.

THE INCIDENCE of bilateral, endophytic uveal melanoma was estimated in 1977 to be one per 50 million whites.[1] Published reports since 1977 indicate, however, a higher incidence.[2-6] Disseminating cutaneous melanoma should be ruled out in cases of bilateral uveal melanoma[7,8] because metastasis or extension of a primary uveal melanoma to the fellow eye is rare.[9] Simultaneous, bilateral, diffuse melanocytic hyperplasia is a rare but well-defined entity that differs from bilateral endophytic uveal melanoma and involvement of the fellow eye in malignant melanoma.[10-14] Because diffuse melanocytic hyperplasia did not metastasize, investigators do not know whether to call it a melanoma[12-14] or a nevuslike lesion.[10,11] We used light and electron microscopy, immunologic techniques, and tissue culture to estimate the biologic characteristics of this condition in the patient we studied.

Case Report

In August 1984, a 52-year-old woman sought our advice because of blurred vision in both eyes for two weeks. Family and personal (general and ophthalmologic) histories were noncontributory. Corrected visual acuity was 20/40 in both eyes. The anterior chambers were flat because of iris cysts and ciliary body cysts, which had the typical appearance when seen with a Goldmann contact lens with the pupil dilated. No solid tumor was noted at that time. The lenses showed the beginning of cataractous changes. Ophthalmoscopic examination disclosed pigmented uveal spots, which were initially interpreted as uveal nevi, and a bilateral macular edema. Fluorescein angiography disclosed breaks in the retinal pigment epithelium without subretinal neovascularization.

The cataracts increased in density and were extracted a few months later (right eye, February 1985 and left eye, March 1985) without complications. The supposed uveal nevi increased in number and diameter (Figs. 1 and 2). With time, visual acuity was reduced and the visual field progressively narrowed. These conditions were attributable to macular degeneration and glaucomatous optic atrophy. In May 1985, a solid tumor was found in the chamber angle of the left eye, and the glaucoma was therefore considered tumor-induced. The iris cysts and ciliary body cysts were thought to have an additional pressure-increasing effect
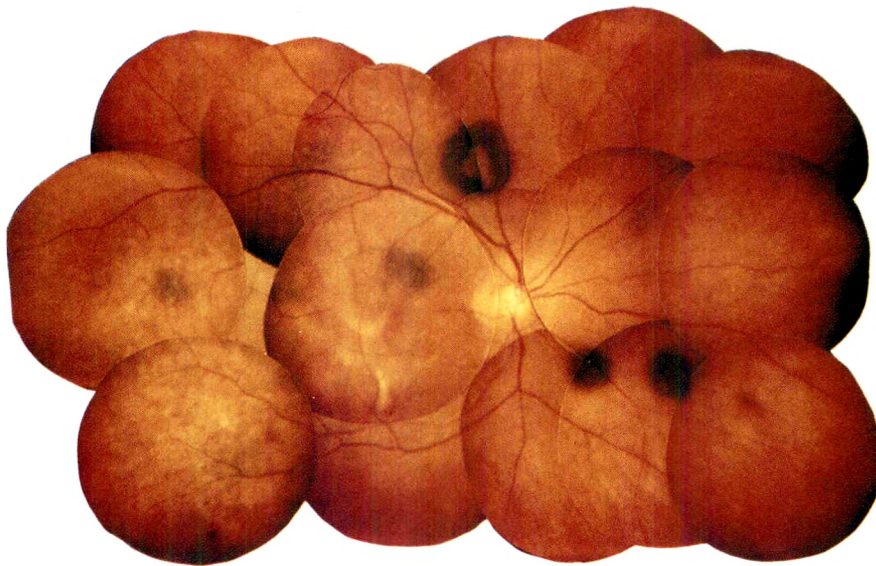
Fig. 1 (Rohrbach and associates). Right eye, August 1985. Note multiple supposed uveal nevi, which correspond to circumscribed hyperpigmentations of the diffuse uveal process. Macular gliosis and optic atrophy as a consequence of a chronic angle closure glaucoma have developed.

because penetration with a Nd:YAG laser resulted in a deepening of the anterior chambers and a temporary reduction of intraocular pressure. Sector iridectomy (right eye, June 1985 and left eye, July 1985), a filtering procedure (right eye, March 1986 and left eye, April 1986), and cyclocryocoagulation (right eye, September 1986 and left eye, May, September, and October 1986), had to be performed to lower the intraocular pressure, which often had risen
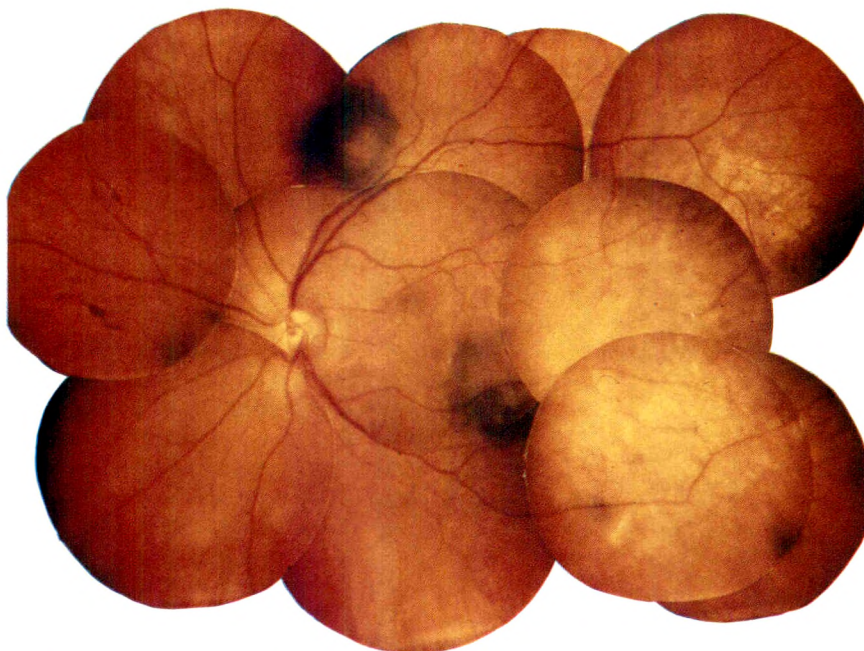
Fig. 2 (Rohrbach and associates). Left eye, August 1985, is similar to the right eye (Fig. 1).
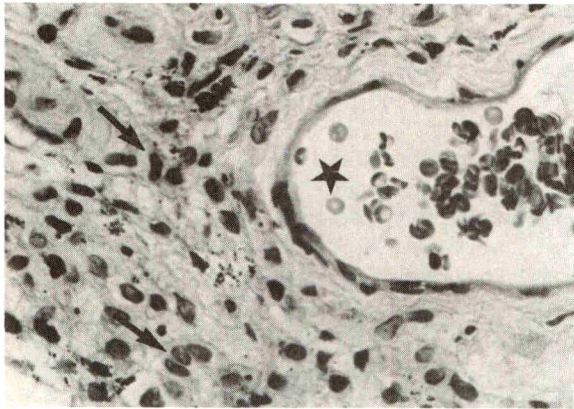
Fig. 3 (Rohrbach and associates). Iris specimen obtained from the left eye in July 1985. The iris stroma is interspersed with round-to-spindled, nevuslike cells (arrows). Note iris vessel with erythrocytes (star) (hematoxylin and eosin, × 600).

to more than 40 mm Hg and could not be controlled by timolol maleate 0.5% twice daily and pilocarpine 2% three times daily, nor by acetazolamide (500 mg/day).

Histologic examination of the iris excised in 1985 showed interspersed nevuslike cells in the stroma (Fig. 3). A definitive diagnosis was not made, but the lesion was assumed to be benign.

In March 1986, the electroretinogram showed a marked reduction of all potentials, and the flicker response indicated advanced cone damage. Computed tomography in November 1986 showed no orbital extension of the tumor. In January 1987, visual acuity had decreased to R.E.: 2/40 and L.E.: light perception, and an extrascleral pigmented tumor, which was subsequently partially removed was seen on the left eye (Fig. 4). Histologic examination again showed a tumor of mostly uniform nevuslike cells with few mitoses and numerous pigment-laden macrophages. Because the extrascleral tumor recurred and enlarged within eight weeks (Fig. 5), enucleation of the left eye was performed in April 1987.

In 1988, the intraocular pressure in the right eye was normal. Exudative detachment of the whole retina and progressive macular degeneration, in addition to the glaucomatous optic cupping, decreased vision to bare light perception. As in the left eye, the tumor could not be demonstrated echographically. Although extrascleral extension was not observed, enucleation of the right eye was advised because of the uncertain nature of the tumor and occasional pain. The patient underwent enucleation in December 1988.

In 1984, results of general medical, gynecologic, and dermatologic examinations were normal except that the patient was overweight with hyperlipidemia and mild arterial hypertension. There was no evidence of a primary or secondary tumor. In 1988, pigmented spots were found in the vulva and in the rectum. Melanoma was suspected, but the histologic diagnosis was a benign pigmented skin lesion. A medical check-up, which included abdominal computed tomography and echography, showed no evidence of a primary or secondary neoplasm. A mild type II diabetes was detected. The isolated rise of gamma glutamyl transpeptidase was attributed to the use of 100 mg/day of fenofibrate. The patient was healthy at her last examination April 1990.
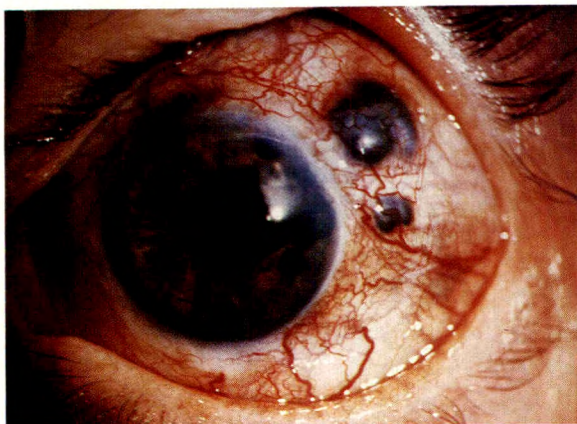
Fig. 4 (Rohrbach and associates). Left eye, January 1987. Note extrascleral nodules of pigmented tumor.
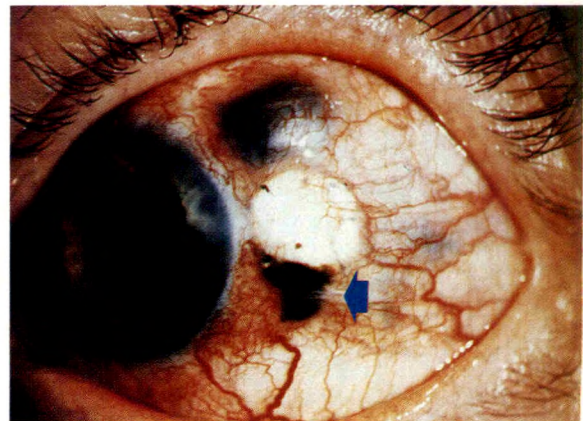
Fig. 5 (Rohrbach and associates). Left eye. Despite excision and scleral patch, extrascleral tumor (arrow) recurred within eight weeks.

Results

Histologic examination disclosed similar features in both eyes. Macroscopic and light microscopic examinations showed that the choroid, ciliary body, and iris were evenly thickened (Fig. 6) by an infiltration of round-to-spindled, uniform cells with only occasional nucleoli (Fig. 7). Mitotic figures were scarce. Some cells had a nuclear fold like the spindle A-cell type described by Callender[15] (Fig. 7). Tumor cells could be found outside the sclera in the left eye (Fig. 8) and within the sclera along a ciliary nerve in the right eye. Circumscribed hyperpigmentations corresponded to the clinically observed uveal nevi. Vessels within the tumor were sparse, but there were no necrotic areas within the tumor. Bone formation had begun at the posterior pole of the left eye, possibly because of tumor-induced chronic damage to the retinal pigment epithelium.[16] The chamber angles were completely occluded by tumor cells, which grew partly on the inner corneal surface, indicating loss of contact inhibition. Iris cysts and ciliary body cysts—probably tumor-induced degeneration products—were lined by pigmented or nonpigmented epithelium (Fig. 9). They were adjacent to regenerating lens masses. Loss of ganglion cells and of retinal photoreceptors, submacular and supramacular gliosis, and advanced excavation of the optic nerve heads were the cause of the visual loss. The retina was detached in the right eye only.
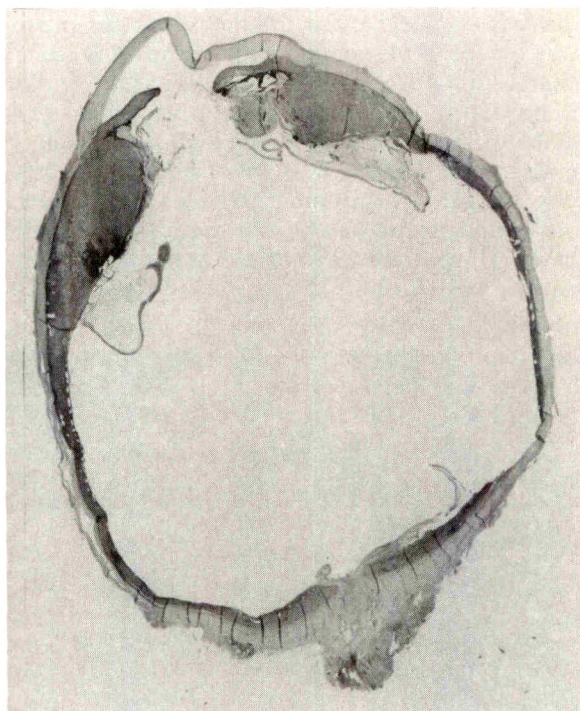
Electron microscopic examination disclosed that the tumor cell nuclei had relatively scant chromatin. Many nuclei were folded, some showed intranuclear vacuoles as a consequence of cytoplasmic invagination, and some had a nucleolus. Well-differentiated mitochondria and rough endoplasmic reticulum, but only few golgi apparatuses (Figs. 10 and 11), were found in the cytoplasm, which had villous processes (Fig. 11). Some tumor cells appeared lighter than others (Fig. 10). Cytoplasmic pigment granules (melanosomes) of different sizes, degrees of pigmentation, and densities seemed not to be coated by a membranous envelope (Figs. 10 and 11). Some tumor cells had cytoplasmic filaments. A few were lined by collagen fibers and a discrete band of homogenous material, which was probably basement membrane. Desmosomes were lacking. Some cells were believed to be pigment-laden macrophages.

Immunologic studies showed that the tumor cells stained positive for S-100 protein indicating a neural crest origin. The tumor cell stains indicated no cytokeratin, nerve filaments, or glial fibrillary acidic protein, making an epithelial or neuroglial process unlikely. Dividing

Fig. 6 (Rohrbach and associates). Right eye prepared for light microscopy. Note diffuse thickening of choroid, and especially of the ciliary body and iris. The retina is completely detached and partly absent because of an artifact. The left eye had similar features.
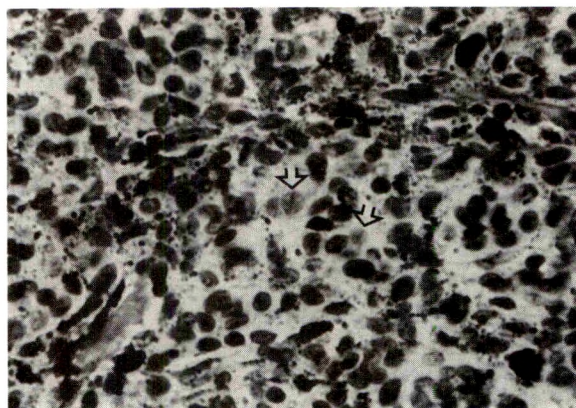
Fig. 7 (Rohrbach and associates). Tumor cells of left eye. Note round-to-spindled cells with rare nucleoli and occasional nuclear folds (arrowheads) (hematoxylin and eosin, × 600).
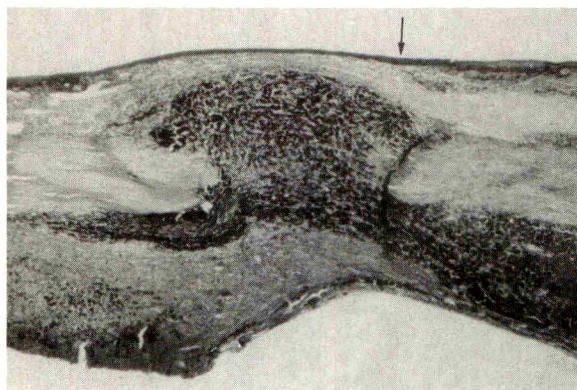
Fig. 8 (Rohrbach and associates). Extrascleral (sub-conjunctival) pigmented tumor in the area of former excision (left eye). Arrow indicates conjunctiva (hematoxylin and eosin, × 25).

Fig. 9 (Rohrbach and associates). Anterior segment of the right eye. Note tumor-induced cystic degeneration of the ciliary epithelium (arrows) (hematoxylin and eosin, × 75).

tumor cells accounted for less than 1% of all tumor cells; less than 1% of cells stained red with the monoclonal antibody Ki-67, which marks all cells outside the G_0-phase of the cell-cycle.[17]

To perform the suspension cell culture, a 3× 5-mm piece of the posterior segment was excised under aseptic conditions and transferred into Hank's balanced salt solution. Sclera and tumor were separated. Because the neoplasm did not invade the sclera, it could easily be separated from it. The tumor was transferred into Hank's buffer, which contained 0.1% trypsin (GIBCO, Berlin, West Germany) and 0.025% collagenase. It was incubated for one hour and dissociated mechanically by repeated suctioning in a Pasteur pipette. After repeated washing in Hank's solution (three times, ten-minute centrifugation at 1,000 revolutions per minute with a centrifuge), the dissociated cells (eight petriperm dishes coated with polylysin and laminin) were transferred to a F12-medium (GIBCO) containing 5% fetal calf serum and incubated in a cell culture incubator at 37 C and in an atmosphere containing 5% CO_2. The medium was exchanged every three days. Cells were observed with an inverted Zeiss microscope and photographed on a black and white TX-pan 400 film. The initial density of the dissociated cells was about 0.4×10^5 to 0.5×10^5 (4×10^4 to 5×10^4). Four dishes were contaminated after one week and discarded. Over an observation period of five weeks, the cells remained in suspension and were spherical without any tendency to attach to the matrix. The cells were uniformly round to oval, black, and varied in size. The largest cells showed typical melanin granulation. The cell density increased over five weeks to 1.1×10^5 to 1.3×10^5 in the four remaining dishes). This increase was continuously observed over the time of culture and was not affected by the addition of basic fibroblast growth factor (prepared from bovine pituitary gland) at concentrations of up to 10 pg/ml of medium. The shape and size of the cultured cells remained unchanged throughout the period of observation.

Discussion

Simultaneous bilateral uveal melanocytic hyperplasia is a rare, but well-defined process that affects middle-aged and elderly white patients and has a female preponderance.[10-14] It has not led to metastasis, and it was arbitrarily classified as a melanoma or as nevus. Because the patients described in published reports had primary extraocular malignant tumor (mostly carcinoma of the abdomen or bowel), a new, oncogenic syndrome was postulated.[10,11,13,14] We know, for example, that cells of skin fibroblasts from patients with hereditary adenomatosis of the colon and rectum behave more like malignant cells in tissue culture.[18] Moreover, non-metastatic diffuse[19] or endophytic[7,20] uveal melanomas have been seen in patients with a preceding cutaneous melanoma or another primary tumor,[7,20] whereas uveal melanoma patients may have an increased risk of developing a second tumor.[7] The conjunction of cutaneous and uveal melanomas is part of the dysplastic nevus syndrome or B-K-mole syndrome.[7,20,21]
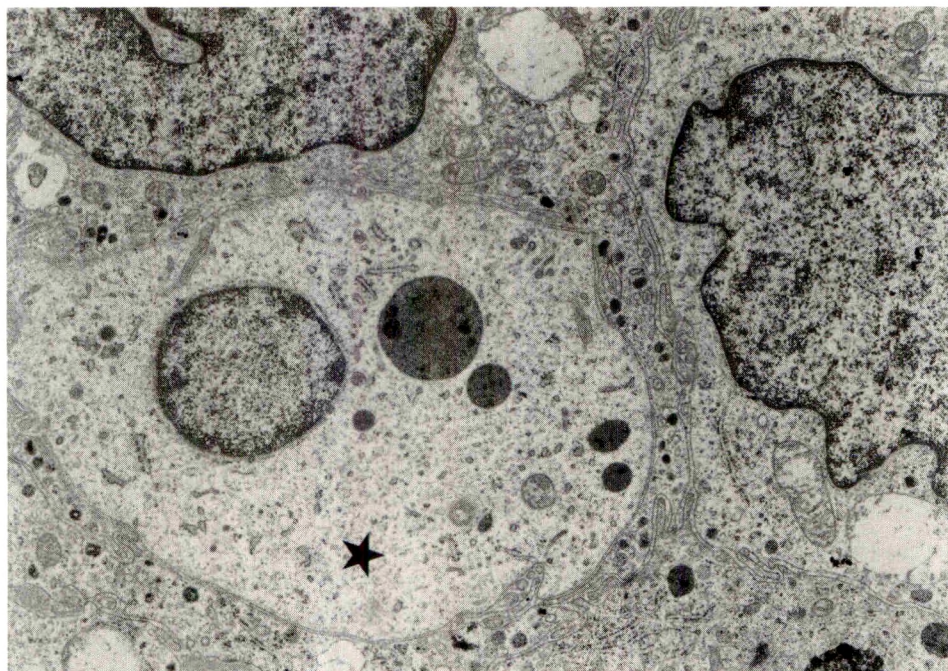
Fig. 10 (Rohrbach and associates). Electron micrograph of a less-pigmented tumor cell (star) from the right eye with pigment granules of different size and scattered rough endoplasmic reticulum. Only few mitochondria (×4,800).
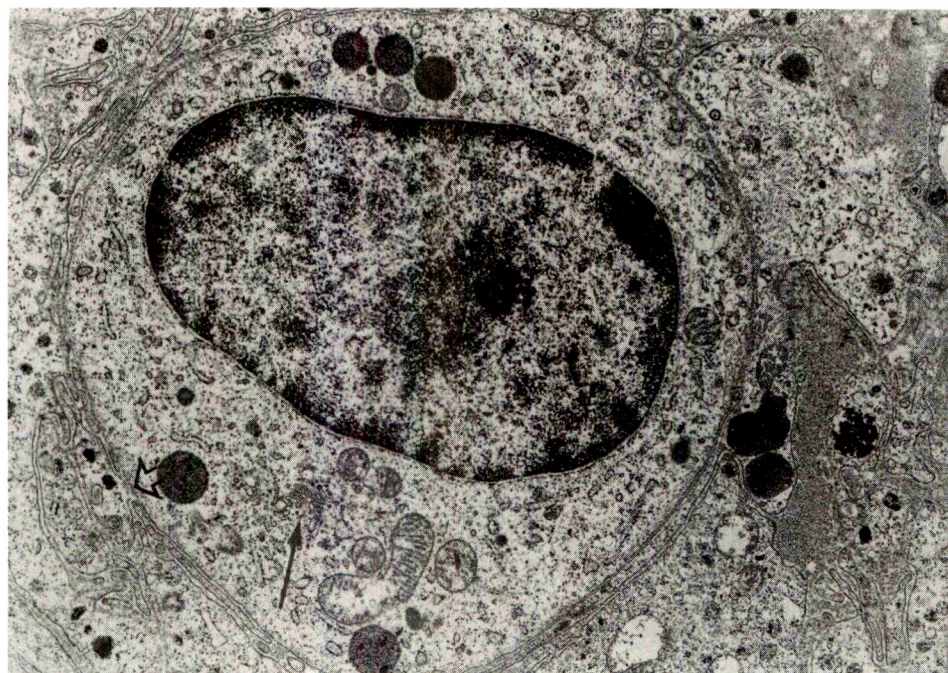
Fig. 11 (Rohrbach and associates). Electron micrograph shows a less-pigmented tumor cell from the right eye with some mitochondria, pigment granules, scattered rough endoplasmic reticulum, and a golgi apparatus (arrow). Cytoplasm shows villous processes (arrowhead) (×4,800).

Therefore, a neoplasm or a neoplastic disposition may alter cells at other sites of the body such that malignant transformations may occur. No extraocular primary tumor could be detected in our patient five years after the onset of visual symptoms. In most reported cases, the associated extraocular tumor caused death within three years of diagnosis of the bilateral, diffuse, uveal process.[10,12,13] It could be, therefore, that the patients' survival time had been too short for the development of metastases from the uveal lesion.

In our patient, the cytologic characteristics were similar to those of patients described previously; there were mostly uniform spindle cells with only rare nucleoli and mitotic figures, and some eyes had varying amounts of epithelioid cells).[10,12-14] The small amount of tumor cells outside the G_0-phase of the cell cycle as demonstrated with the monoclonal antibody Ki-67, and the absence of metastases after five years of observation (diffuse melanomas usually have a poor prognosis[22]), indicate, though are not proof of, a benign, nevuslike process. Alternatively, infiltrative growth (in the chamber angle[10,12,14] and on the posterior corneal surface), scleral invasion[10,12-14] and perforation,[10] (Figs. 4, 5, and 8) as well as growth of tumor cells in suspension tissue culture make a malignant tumor more probable. Our final diagnosis was simultaneous, bilateral, diffuse uveal melanoma of low growth potential.

We conclude that because the bilateral diffuse uveal melanocytic lesions, whether they are melanomas or not, grow simultaneously in much the same way and because they are often associated with an extraocular primary tumor (carcinoma), the assumption of an oncogenic process is justifiable. Additionally, the diffuse tumor could be a consequence of diffuse melanocytic transformation (except in areas such as the chamber angle or posterior corneal surface, where normally no melanocytes exist) rather than of a diffuse, invasive growth. Even an extrascleral tumor may be caused by extrascleral transformation (for example, Schwann cells of ciliary nerves) and not by a real scleral penetration of the tumor extending from the interior of the globe.[12] The boundary between benignancy and malignancy is not a sharp line but a broad zone, and whether a tumor is benign or malignant sometimes cannot be determined with the methods available. At present, therefore, the biologic character of certain tumors in the transition zone between nevi and

melanomas can be ascertained only by the clinical course. The challenge of future work in this field is in the development of new techniques such as immunologic detection of malignancy-specific antigens and molecular probes.

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OPHTHALMIC MINIATURE

"Wonderful dark eyes," he said.

She didn't know where to look. His pale eyes held her like a pinned butterfly. Looking into them was like looking up at the sky, trying to see through wispy clouds to the end of it. Once she'd tried that, lying on her back for hours until her eyes smarted and she felt dizzy. She was feeling dizzy now.

Johanna Kingsley, *Faces*
New York, Bantam Books, 1987, p. 26

The Gradient Filter Test to Assess Amblyopia

Ronald V. Keech, M.D., and Pamela J. Kutschke, B.S.

A new technique, the gradient filter test, was developed for evaluating changes in the visual acuity of preverbal children undergoing treatment for amblyopia. The gradient filter test consists of a series of calibrated photographic fog filter and prism lenses. The combined prism-filter lenses are placed in front of the normal fixing eye. The greatest density (fogging value) filter that causes a switch in fixation from the amblyopic to the normal eye is noted. In both normal eyes of 20 nonamblyopic patients and the fellow (nonamblyopic) eyes of 20 amblyopic patients, visual acuity decreased as the density of the prism-filter lens increased. The gradient filter test accurately detected an improvement in visual acuity when compared with optotype measurements in eight patients undergoing occlusion therapy. The gradient filter test is a useful clinical tool that can assess changes in visual acuity in preverbal children who are being treated for amblyopia.

THE FIXATION PREFERENCE TEST[1,2] is commonly used in clinical practice to diagnose and monitor amblyopia in preverbal children. It indirectly assesses visual acuity by determining a patient's preference for fixation in one eye as compared with the fellow eye. A significant disadvantage of this test is its inability to precisely detect changes in visual acuity. Amblyopic patients who are unable to maintain fixation with the fixation preference test may exhibit large differences in the visual acuity of their amblyopic eye with other measures. When vision is improved with patching, descriptions such as "holds for a few seconds" or "holds through a blink" are imprecise, subjective guides to the presence of a visual acuity change.

The establishment of a treatment end point with the fixation preference test is also difficult. The preferred response is equal fixation. This may not be possible, especially in the presence of a unilateral organic disorder that prevents normal vision.

One of us (R.V.K.) developed a new technique, the gradient filter test, for measuring changes in visual acuity in preverbal children. The gradient filter test uses a series of calibrated fog filters to equalize the fixation response between the normal and the amblyopic eye. By comparing the density of the filter required to balance the fixation on different examinations, the gradient filter test detects changes in visual acuity in preverbal children undergoing patching therapy for amblyopia.

Material and Methods

The lens system used in this study consisted of a series of 12-prism diopter prisms and fog filters mounted together in a plastic housing (Fig. 1). The filters are clear photographic fog lenses that are commercially available in densities (fogging values) from one to five in steps of one. In this study, fog filters ranging in density from three to 12 in steps of one were used except for filter density No. 11, which was excluded. Fog filter densities greater than five were achieved by combining two or more fog filters. A 12-prism diopter prism was added to each filter or combination of filters to induce a vertical tropia and make the test useful for patients with or without strabismus.[3,4]

All patients underwent complete ophthalmologic and orthoptic examinations. Patients were considered to have normal vision if they had a best-corrected visual acuity of 20/25 or greater in each eye with no previous history of amblyopia. Patients were considered to have unilateral amblyopia if they had a best-corrected visual acuity in one eye less than 20/30 but greater than 20/200 with no apparent organic cause, and a best-corrected visual acuity in the other eye of 20/25 or greater.
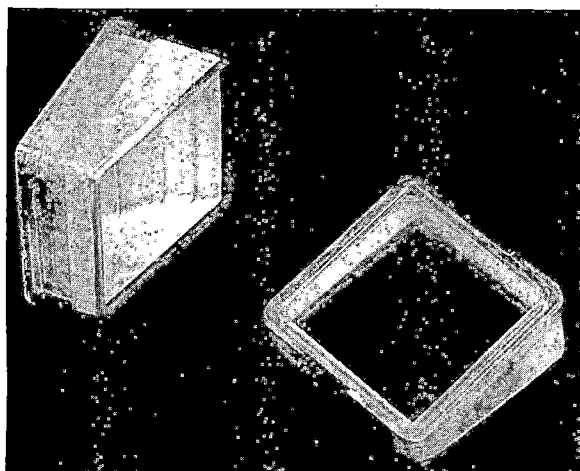
Fig. 1 (Keech and Kutschke). Photographic fog filter and 12-diopter prism mounted in a plastic housing.

The best-corrected visual acuity through each prism-filter lens was recorded in a standardized manner for both eyes of patients with normal vision and for the fellow (nonamblyopic) eye of patients with unilateral amblyopia. The visual acuity was measured for each eye with a Snellen chart at 20 feet. The No. 12 prism-filter lens was placed over the right eye while the left eye was occluded and the patient asked to read the smallest isolated line of letters possible. Previous testing showed that the visual acuity through the prism-filter lenses could improve slightly with time. Therefore, all patients were given no more than ten seconds to complete the line of letters with each lens. The test was repeated with progressively less dense prism-filter lenses until the visual acuity through all nine lenses was recorded. The left eye was measured in the same manner. A separate group of patients with normal vision had both eyes tested as described. Additionally, the test was repeated at least one day later by the same examiner who had no access to the results of the first test.

The visual responses of eight children undergoing occlusion therapy for amblyopia were assessed with the gradient filter test. Five of the children were also tested with the induced-tropia version of the fixation preference test.[3] The gradient filter test and fixation preference test were performed by the same examiner. A second examiner assessed amblyopia in the children on the same visit by using optotype methods. Five of the children were tested with visual

acuity cards,[5] one with Allen pictures,[6] one with tumbling Es, and one with Snellen letters. Each examiner was masked to the results of the other examiner.

Fixation for the gradient filter test and fixation preference test was obtained with an animated toy or a video cartoon[7] placed 20 feet from the patient. The gradient filter test was performed by placing an occluder and the No. 12 prism-filter lens over the fellow (nonamblyopic) eye, removing the occluder, and observing the fixation pattern. The procedure was repeated with filter lenses of progressively less density until fixation switched to the fellow eye or alternated between the amblyopic and fellow eye. The prism-filter lens used at the switch in fixation or alternation was recorded. The gradient filter test, fixation preference test, and the optotype vision tests were repeated on the same patient after one or more patching episodes. A patching episode was defined as a period of full-time occlusion from one examination to the next. This time period was approximately one week for each year of the child's age up to a maximum of four weeks.

Snellen visual acuities were converted to the logarithm of the minimal angle of resolution (LogMar)[8] for statistical analysis. The visual acuities through each prism-filter lens for the 40 normal eyes and the 20 fellow eyes were compared by using the Wilcoxon test. The reproducibility of the visual responses through the prism-filter lenses for 20 normal eyes of ten patients was analyzed by determining the kappa statistic (nonparametric interclass correlation) for the 180 paired observations.

Results

The visual acuity through each prism-filter lens was evaluated for both eyes of 20 patients (mean age, 8 years 5 months) with normal vision and for the fellow eye of 20 patients (mean age, 10 years 7 months) with unilateral amblyopia (Fig. 2). With the exception of prism-filter lens No. 7 (P = .0490), there were no significant differences (P = .093 to .91) in the visual acuities with a given prism-filter lens between the eyes with normal vision and the fellow eyes of the amblyopic patients. The median visual acuity for the group of normal eyes and fellow eyes decreased in a stepwise fashion as the density of the filter increased. Further-
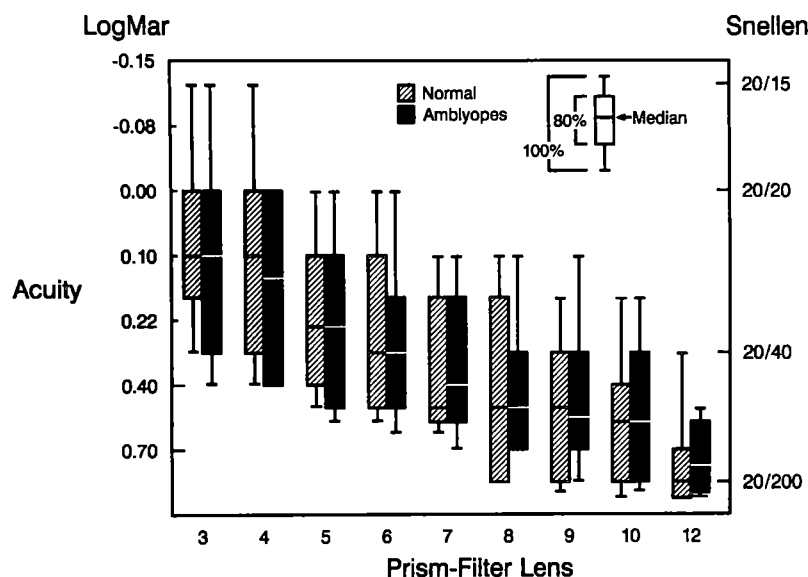
Fig. 2 (Keech and Kutschke). The median and range of visual acuities for the group of 40 normal eyes and 20 fellow (nonamblyopic) eyes for each prism-filter lens.

more, the reciprocal relationship between increasing filter density and decreasing visual acuity was consistent for each patient within both groups.

Although the mean visual acuity was similar for each group, there were wide and overlapping visual acuity ranges between prism-filter lenses for both the normal and fellow eyes. This overlap also occurred when the predicted visual acuity (± 2 S.D.) with each prism-filter lens was calculated for a new patient by using the visual acuity data from the 40 normal eyes (Table).

Reproducibility of the visual acuity measurements through each prism-filter lens was assessed by comparing the first and second observations for both normal eyes of ten patients (mean age, 28 years 5 months) (Fig. 3). There was no difference in the visual acuity measurements of paired observations in 73 of 180 (41%), a one-line difference in 70 of 180 (39%), and more than a two-line difference in only 13 of 180 (7%). For the 180 visual acuity measurements, the probability of the matched pairs being within one Snellen line of visual acuity was 0.7947 (K = 0.718, P < .0001).

The gradient filter test was compared with the induced-tropia version of the fixation preference test and with optotype tests in eight amblyopic children (mean age, 2 years 4 months) undergoing occlusion therapy. Vision was assessed on two different examinations in four patients (four patching episodes) and three dif-

ferent examinations in four patients (eight patching episodes). The gradient filter test detected an improvement of vision in the amblyopic eye in nine episodes and no change in three episodes. The gradient filter test results agreed with the optotype methods in ten of the 12 episodes (Fig. 4). In two episodes, the gradient filter test did not detect an improvement noted by the optotype tests. Visual acuity improved with patching from 20/60 to 20/50 with linear Es in one patient and from 20/60 to 20/40 with Allen pictures in another. The fixation preference test failed to detect any change in visual acuity in the five patients (five patching episodes) tested, although an improvement

TABLE
PREDICTED VISUAL ACUITY RANGE FOR A NEW OBSERVATION IN 40 NORMAL EYES

PRISM-FILTER LENS	SNELLEN VISUAL ACUITY (MEAN)	PREDICTED VISUAL ACUITY RANGE (± 2 S.D.)
3	20/26	20/17–20/39
4	20/27	20/16–20/45
5	20/34	20/19–20/60
6	20/40	20/18–20/72
7	20/48	20/27–20/85
8	20/67	20/23–20/198
9	20/78	20/23–20/265
10	20/99	20/24–20/415
12	20/199	20/176–20/671
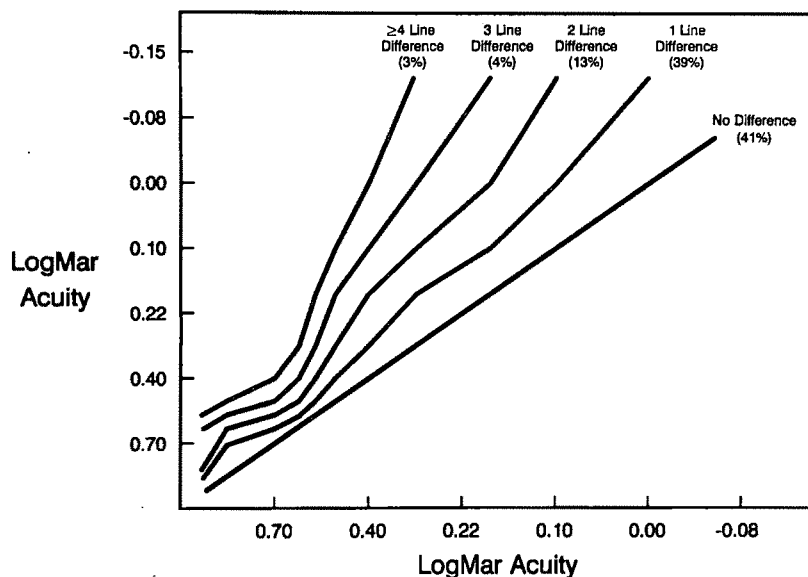
Fig. 3 (Keech and Kutschke). Comparison of the first and second observation of LogMar visual acuity of 20 normal eyes through each prism-filter lens. Each line represents differences in Snellen lines of visual acuity. The probability of a one Snellen line or less difference between matched pairs for the 180 pairs of observations was 0.7947 (K = 0.718, P < .0001).

was noted in all five episodes by the gradient filter test and the optotype tests.

Discussion

The gradient filter test was developed as a simple method to assess changes in visual acuity with occlusion therapy accurately. This study demonstrated a consistent relationship between the level of vision and the density of the filter. For every patient tested, the visual acuity of normal eyes and the fellow eyes of unilateral amblyopic patients decreased as the density of the prism-filter lens increased. A change in the prism-filter lens in front of the fellow eye necessary to switch or alternate fixation between the normal and the amblyopic eye, therefore, strongly suggests a change in the visual acuity of the amblyopic eye. This assertion is also supported by the results in children undergoing occlusion therapy for amblyopia. In ten (83%) of 12 patching episodes, the improvement in visual acuity measured by optotype methods was accompanied by a decrease in the prism-filter lens density required to cause a switch in fixation.
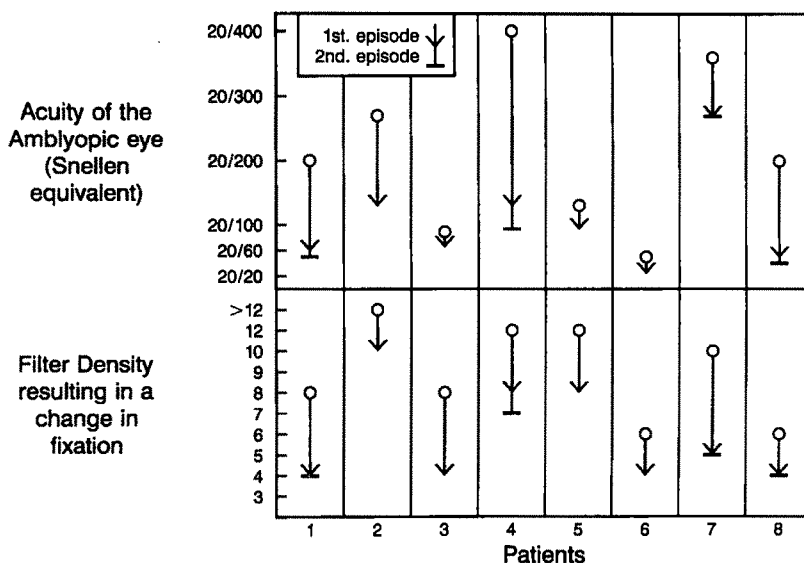
Fig. 4 (Keech and Kutschke). A comparison of the ability of the gradient filter test and optotype vision tests to determine a change in visual acuity after one or more episodes of occlusion therapy.

The reproducibility of the gradient filter test also confirms its value as a clinical test. Visual acuities obtained from the same eye with the same prism-filter lens varied by only one Snellen line or less in 143 (79.4%) of the 180 paired observations in 20 normal eyes tested. Although not testable in preverbal children, it is unlikely that the reproducibility would vary with age.

In this study, we found that the difference in the density (fogging value) between each consecutive filter was slight and that it was clinically more useful to rely on a change in density of two or more prism-filter lenses before concluding that a change in visual acuity had occurred with occlusion therapy. A new version of the gradient filter test now includes only five lenses with a greater difference in consecutive filter strength.

Other lens filter systems have been described for the assessment of amblyopic patients. Bagolini[9] used a graded red filter bar for estimating the depth of suppression in patients with suppression scotomas with or without amblyopia. Other investigators[10,11] developed a set of neutral-density filters that aid in detecting and grading the severity of afferent pupillary defects in patients with various disorders, including amblyopia. Cadera and associates[12] used a neutral-density rotary filter in combination with a fixation preference test to calibrate the point at which a patient would switch fixation from the fellow eye to the amblyopic eye. Although similar to the gradient filter test, their test is difficult to perform in young children and is useful only in patients with a manifest deviation. Additionally, their results were not analyzed statistically.

The gradient filter test was designed to accurately identify a change in visual acuity with occlusion therapy rather than to predict the value of a single visual acuity or to determine the precise change in visual acuity. As shown in the Table, the visual acuity range through any prism-filter lens for a patient is too large to be clinically useful. The gradient filter test, however, appears to be sensitive to changes in visual acuity induced by occlusion therapy and should be a useful clinical tool for examining amblyopic patients.

The value of the gradient filter test lies in its ability to provide the clinician with immediate and reliable evidence about the success of occlusion therapy when other methods are not helpful. Fixation pattern tests are easy to perform, but they lack accurate methods for assessing visual improvement. Forced-choice preferential looking methods, even in the simplest form, are cumbersome, time-consuming, and not suitable for all children. The gradient filter test is faster and easier to perform than forced-choice preferential methods and offers a more precise guide for monitoring visual changes than traditional fixation pattern techniques in preverbal children undergoing occlusion therapy.

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The Use of Crossed Polarized Filters in the Measurement of the Relative Afferent Pupillary Defect

Michael L. Rosenberg, M.D., and Armando Oliva, M.D.

We used crossed polarized neutral density filters to quantitate relative afferent pupillary defects. To prove reproducibility, the relative afferent pupillary defects of 20 patients were measured with this technique by two independent observers. There was no statistically significant difference between the two measurements. Relative afferent pupillary defects as low as 0.03 log unit were easily measured. These filters offer a convenient and reproducible technique that is more sensitive than the use of neutral density filters.

THE USE OF NEUTRAL DENSITY FILTERS to measure the relative afferent pupillary defect has been described.[1-6] Quantitation of the relative afferent pupillary defect is useful in the serial evaluation of patients, as well as for comparing the size of the relative afferent pupillary defect with other elements of optic nerve function. We used polarizing filters to measure the relative afferent pupillary defect and confirmed the technique's reproducibility between different observers.

Material and Methods

The instrument used to measure the relative afferent pupillary defect consists of a trial lens

spectacle on which two sets of polarizing filters have been mounted (Fig. 1). The first set is fixed over each eye with the axis of polarization oriented horizontally. The second set is mounted directly over the first. Its axis of polarization can be rotated from 0 to 180 degrees. At 0 and 180 degrees, maximum light transmission through the filter is obtained. At 90 degrees, minimum light transmission occurs. The amount of light transmission at 5-degree increments was measured empirically for two sets of such spectacles with no difference between the two (Fig. 2).

The relative afferent pupillary defect can be measured simply by repeatedly testing for the defect, decreasing the amount of light shone into the normal eye after each observation. This is done by rotating the filter over the normal eye between each test. When the relative afferent pupillary defect can no longer be seen (that is, when the initial constriction and redilation of each pupil is symmetric), the axis of the filter is taken as the measure of the relative afferent pupillary defect in degrees. The closer the value is to 90 degrees, the more severe the relative afferent pupillary defect. It is useful to surpass the end point, creating a relative afferent pupillary defect on the opposite side, bracketing the end point across a narrow range. To confirm small relative afferent pupillary defects, a technique similar to that described for neutral density filters is used. One can rotate the filter 10 to 15 degrees over the eye and look for a relative afferent pupillary defect. The test is then repeated on the other eye. The abnormal eye will have a more easily seen relative afferent pupillary defect, whereas the normal eye will not have the expected relative afferent pupillary defect.[3]

To test the reproducibility of this technique, we examined 20 patients who had optic neuropathies and relative afferent pupillary defects. The relative afferent pupillary defect was measured on each patient independently by two observers during the same patient visit, without either observer having knowledge of the side or the degree of defect found by the other observer. Special care was taken to keep

Fig. 1 (Rosenberg and Oliva). Left, Crossed polarizing filter glasses. Right, Lateral view shows the technique used for the testing of an afferent pupillary defect. Touching the filters with the light decreases glare and allows a more constant distance between the light source and the pupil.

variables that may affect the measurement of the relative afferent pupillary defect as constant as possible. The examination room was kept completely dark during all measurements. Occasionally, a dim light was placed as a fixation target at the end of the room. The light of a standard, fully charged halogen transilluminator was used for all tests. After a maximum of three to five swings of the illuminator, testing was stopped and each eye was illuminated beneath the filters. If an end point was not reached after several tests, the room lights were turned on and the spectacle reset to 0 degrees to avoid differential bleaching of the two retinas. The lights were again turned off, and the filter was rotated to the new suspected value. The light was allowed to touch the filter to ensure equal distance between the light and each eye and to eliminate glare for the observer (Fig. 1). Oblique illumination of the eyes was avoided, and the light was not held longer over one eye than over the other eye.

Results

The values for the relative afferent pupillary defect in seven patients were found to be identical by the two observers (Table). Only two

patients had measurements that differed by more than 10 degrees. The calculated mean difference between the two observed measurements was 6.5 degrees (S.D., 7.7). Similarly, the difference in light transmission needed to neutralize the afferent pupillary defect differed by more than 0.2 log unit in only two patients. The mean difference between the two observers was 0.07 log unit (S.D., 0.08). The paired t-test analysis disclosed no significant difference between the measurements with either the log units or the difference in degrees of measurement (P > .4).

Discussion

The relative afferent pupillary defect is one of the most sensitive indicators of asymmetric optic nerve function. It is more sensitive than the visual-evoked potential or the pupillary cycle time.[7] Most frequently, relative afferent pupillary defects are described by using a qualitative 1 to 4+ scale. Unfortunately, this scale lacks the quantitation that is necessary for follow-up and comparison to other measures of optic nerve function. The use of neutral density filters offers a way to quantify and standardize measurements.[1-6] The main drawback of this
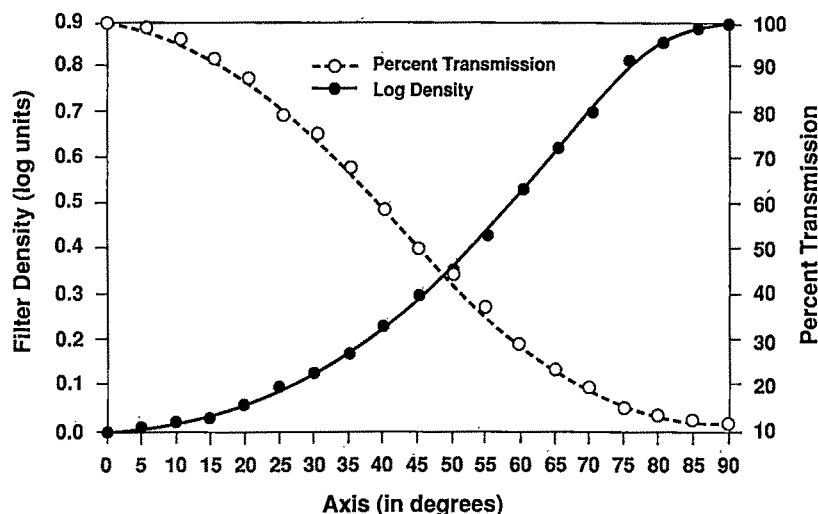
Fig. 2 (Rosenberg and Oliva). Light transmission through polarized filters (all transmission measured in foot-candles).

technique is that the filters come in discrete log units (in increments of either 0.1 or 0.3). In contrast, the crossed polarizing filters provide a continuous scale for measurement, which allows the examiner to easily bracket the relative afferent pupillary defect, usually across a narrow range. Whereas 0.3 log unit is the smallest

TABLE

MEASUREMENT OF RELATIVE AFFERENT PUPILLARY DEFECT

| PATIENT NO. | RELATIVE AFFERENT PUPILLARY DEFECT (DEGREES) | | LOG DIFFERENCE |
	OBSERVER 1	OBSERVER 2	
1	45	25	0.20
2	55	60	0.10
3	45	45	0
4	55	55	0
5	45	35	0.13
6	30	30	0
7	60	60	0
8	65	55	0.19
9	30	20	0.07
10	50	50	0
11	45	35	0.13
12	20	15	0.02
13	30	20	0.03
14	25	25	0
15	60	60	0
16	65	70	0.09
17	55	35	0.26
18	25	35	0.07
19	50	40	0.12
20	30	25	0.03

relative afferent pupillary defect that can be measured with confidence using neutral density filters,[3,4] it is relatively easy to measure relative afferent pupillary defects of 0.03 to 0.06 log unit (15 to 20 degrees) with our technique.

The sensitivity of this test depends on many factors. Characteristics of the individual patients, such as iris color and pupillary reactivity, affect the ease with which one can evaluate the asymmetry of the pupillary response. Dark irides make measurements difficult at higher degrees of deficit. At any setting, sluggish pupils were more difficult to evaluate.

In many patients with briskly reactive pupils and light colored irides, afferent pupillary defects of 10 degrees (0.02 log unit) were easily measured with a high degree of confidence. In patients with less briskly reactive pupils and darker irides, however, a 0.1-log unit relative afferent pupillary defect might be all that could be measured. Rarely, we were unable to define an end point in a patient with abnormally sluggish pupils.

The severity of the afferent pupillary defect has a more complex effect on our ability to obtain accurate measurements. One would expect, based on the nonlinearity of the filters, that accuracy and consistency would be highest between 55 and 75 degrees. Smaller changes within this range produce a much greater percentage change in light transmission than do similar changes at lower or higher settings. As the filters darken, it becomes harder to see the pupil and one must look for constriction of the opposite pupil. Thus, even though the percent change might be higher between 60 and 65 degrees, the ability to see a small pupillary

escape was greater at lower settings. These factors seemed to result in a relatively constant accuracy at all settings.

The difference in sensitivity for measuring a relative afferent pupillary defect between this technique and that using neutral density filters is striking (0.3 log unit vs 0.03 log unit). We suspect that this is at least in part attributable to the decrease in light transmitted to each eye with the crossed polarized filter technique. Even at 0 degrees, there is a fivefold decrease in the amount of transmitted light to each eye. It has been our experience, as well as that of others,[3,8] that relative afferent pupillary defects may be easier to see with a dimmer light source. We have also noted that in some patients a questionable relative afferent pupillary defect without the filters becomes more obvious when the patient is tested with the filters on and set at 0 degrees over both eyes. For this reason, we have begun to test all patients with both a bright and a dim light. We believe there is a significant increase in positive tests with a dimmer light.

Practically, the spectacles eliminate the need for multiple filters of different light transmittance. The spectacles also allow the examiner to place a +10.0-diopter lens over each eye, providing magnification of the pupillary reaction. One drawback to these filters is that 0.9 log unit (90 degrees) is the maximum relative afferent pupillary defect that can be measured. Some patients with marked optic neuropathies and large relative afferent pupillary defects are thus off the scale. Placing a standard neutral density filter over the polarized filter would easily cor-

rect this problem. Shifting the scale downward would allow larger relative afferent pupillary defects to be measured accurately. The scale, using a 0.3-log unit filter for example, would range from 0.3 log unit (at 0 degrees) to 1.2 log units (at 90 degrees).

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Hydroxyamphetamine Mydriasis in Normal Subjects

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Hydroxyamphetamine eyedrops are used to help localize the lesion in Horner's syndrome. Because normal variability in the response to the eyedrops may influence the interpretation of test results in patients with Horner's syndrome, we studied both the interocular variability of the drug's mydriatic effect within each normal subject and the variation between individuals. We used photographs to document the variability among 26 normal subjects. Hydroxyamphetamine hydrobromide 1% eyedrops (Paredrine) were placed in both eyes of normal subjects in the same way that patients with Horner's syndrome are tested. The drug produced a mean increase in pupil size of 1.96 mm (± 0.61 S.D.) in the 52 eyes tested. In normal subjects, the mydriatic effect of hydroxyamphetamine was symmetric in each pair of eyes. The mean interocular asymmetry of mydriasis as measured by the difference in dilation (right eye dilation minus left eye dilation) was −0.087 mm (± 0.29 S.D.). Thus, the variability of hydroxyamphetamine mydriasis from one eye to the other in a single subject was much lower than the variability between subjects.

PAREDRINE (parahydroxyamphetamine hydrobromide 1%) was introduced as a mydriatic eyedrop in 1937.[1,2] It was first used in combination with atropinic agents in an effort to hasten patients' recovery from cycloplegia and then as a gentle mydriatic.[3] In the 1940s, it was a popular nasal decongestant and was used with a sulfathiazole suspension to treat sinus disease.[4] It was also used to treat cardiogenic shock[5] and cardiac arrhythmias,[6] and was shown, unlike amphetamine sulphate, to have little or no effect on the central nervous system.[7] In the mid-1960s, it was concluded that, like tyramine, its adrenergic action resulted from the release of norepinephrine from nerve endings.[7-9] In 1971, it was suggested[10] that because of its mode of action, hydroxyamphetamine might be useful as a diagnostic test to localize the lesion in Horner's syndrome. It has been repeatedly observed that hydroxyamphetamine causes less dilation of the affected pupil in Horner's syndrome when the lesion is in the postganglionic neuron,[10-13] but does dilate the affected pupil in preganglionic lesions. This effect has been demonstrated in cases of surgically placed lesions in humans[10] and rabbits.[11] In recent years, hydroxyamphetamine has replaced epinephrine as the most reliable pharmacologic tool for identifying a postganglionic lesion in Horner's syndrome.

When used as a diagnostic test for Horner's syndrome, hydroxyamphetamine is placed in both eyes and the pupillary response is noted 45 to 60 minutes later. Many factors deserve consideration when evaluating the localizing value of hydroxyamphetamine in Horner's syndrome. We evaluated the influence of the following factors: the variability of hydroxyamphetamine mydriasis among individuals; the symmetry of hydroxyamphetamine mydriasis between the two eyes of an individual; and the effect of patient age and iris color on hydroxyamphetamine mydriasis. We have attempted to define the normal range of hydroxyamphetamine mydriasis that would be expected under the conditions of testing used in Horner's syndrome.

Subjects and Methods

Twenty-six normal subjects were used. None had any history of migraine headaches. Their mean age was 50.1 years (S.D. ± 15.8 years; range, 19 to 69 years). Hydroxyamphetamine (1%) was placed into the conjunctival sac of each eye, both eyes were wiped, and 20 to 40 seconds later, in an effort to balance the dose in the two eyes, a second drop was placed in each eye. Photographs were taken just before the eyedrops were given and 45 to 60 minutes after instillation. The photographs were taken with a Loewenfeld-Rosskothen camera[14] at 1:1 magnification using Polaroid film in moderately bright light. The pupil diameters of both eyes were measured directly from these photographs to the nearest tenth of a millimeter with a magnifying ruler.

We considered two kinds of variability in hydroxyamphetamine mydriasis, variation between individuals and variation between the eyes of one individual.

For the former, we measured the amount of mydriasis produced by hydroxyamphetamine in each of the 52 eyes of the 26 normal subjects by subtracting the predrop pupil size from the postdrop pupil size. From this, the mean mydriasis for the right and left eyes was calculated. The standard deviation of this mean represented the interindividual variation in mydriasis. We also investigated the effect of age and iris color (blue and green vs brown) on degree of mydriasis.

For variation between eyes of a given individual (the interocular variation) in mydriasis, we plotted pupillary diameter for each subject's right eye, both before and after hydroxyamphetamine, against the corresponding pupillary diameter of the left eye to find whether hydroxyamphetamine produced significant anisocoria in normal subjects. Additionally, the dilation difference between the two eyes (mydriasis of the right eye minus mydriasis of the left eye) was calculated to quantify the interocular asymmetry. The contribution of measurement error was also evaluated by comparing the dilation difference between the two eyes as measured from photographs by two different observers.

Results

The mean pupillary dilation to hydroxyamphetamine for the combined 52 eyes was 1.96 mm (S.D. ± 0.61 mm), with a range of 0.5 to 3.1 mm (Fig. 1). The mean pupillary dilation of the right eyes was 1.94 mm (± 0.63 S.D.), and the mean dilation of the left eyes was 1.99 mm (± 0.68 S.D.) for the 26 normal subjects.

No effect of age on hydroxyamphetamine mydriasis was found (Fig. 2). Additionally, no significant difference (P = .40) in mean mydriasis was observed in eyes of differing pigmentation (blue and green eyes, mean dilation = 2.04 ± 0.68 mm [N = 11 white subjects, 22 eyes]; brown eyes, mean dilation = 1.90 ± 0.55 mm
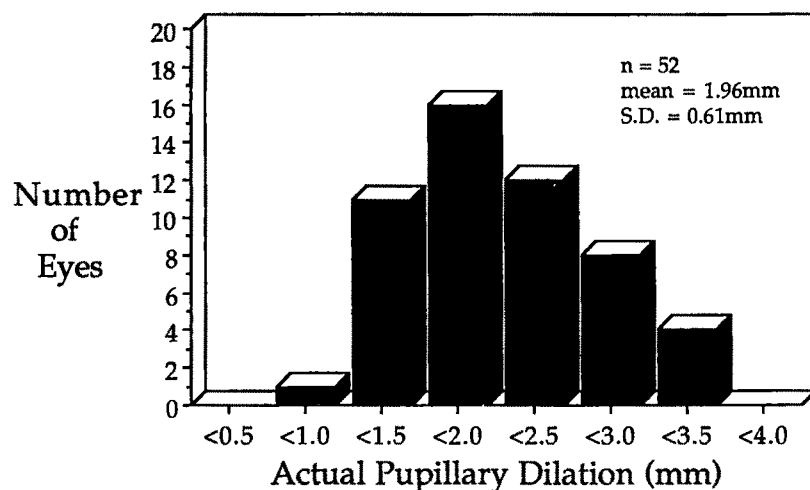
Fig. 1 (Cremer and associates). Histogram shows the actual pupillary dilation in all 52 eyes (26 normal subjects) (mean = 1.96 ± 0.61 mm).
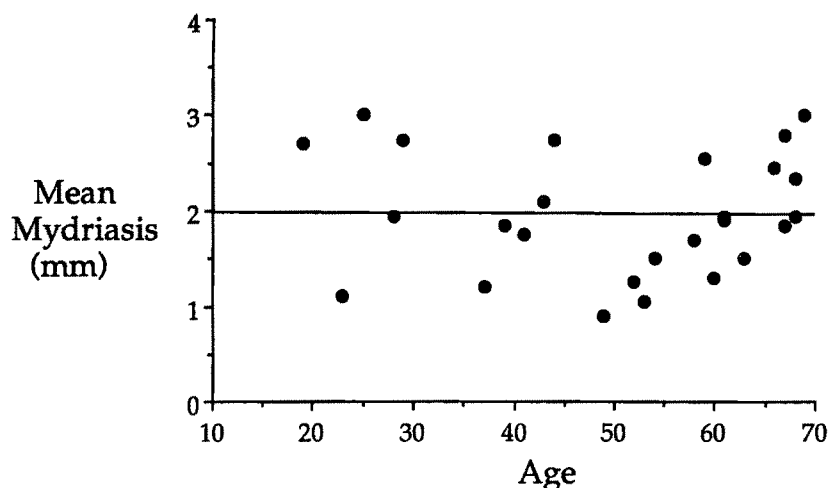
Fig. 2 (Cremer and associates). Regression shows the lack of relationship between age and the mean mydriasis (average of right and left eye mydriasis for each individual) when using two drops of 1.0% hydroxyamphetamine hydrobromide (correlation coefficient [r] = 0.0).

[N = 15 subjects, 13 white, two oriental, 30 eyes]).

The plot of diameter of the right eyes contrasted with diameter of the left eyes is shown both before and after the administration of hydroxyamphetamine in Figure 3. The graph shows that when hydroxyamphetamine is placed in both eyes of a normal individual, it generally does not produce an anisocoria. Additionally, the mean difference in dilation between the two eyes was only -0.087 mm $\pm$ 0.299 S.D. Thus, we found that the right eye to left eye variation in mydriasis was much less than variation from one person to another.

The proportion of interocular variability attributable to measurement error was found to be 23.7% (95% confidence interval = 11.4% to 45.7%). Almost one fourth of the interocular response variability to hydroxyamphetamine could be accounted for on the basis of measurement variability from the photographs.

Discussion

The results of our study help clarify what the anticipated response to hydroxyamphetamine will be in normal individuals. It is important to know how much difference in mydriasis is to be expected between the two eyes of a normal individual if this difference is to be used as a localizing test in Horner's syndrome. We found little interocular difference in the hydroxyamphetamine mydriasis (mean = -0.087 mm $\pm$ 0.299 S.D.), which indicates that when a difference is found, the test should have diagnostic

value. Our conclusions support those of van der Wiel and van Gijn[13] (mean = 0.0075 mm $\pm$ 0.30 S.D.).

We demonstrated that the degree of hydroxyamphetamine mydriasis varies among individuals. Factors that may influence the degree of apparent hydroxyamphetamine mydriasis include difference in the level of alertness at the beginning and end of the test (a person who becomes sleepy by the end of the test might exhibit less mydriasis); differences in the penetration of hydroxyamphetamine through the cornea; the amount of norepinephrine stores in nerve endings available for release; and the number of adrenergic receptors on the dilator muscle. In our normal subjects, these factors produced little, if any, interocular differences in response and must have exerted a relatively symmetric effect on the two eyes. Despite the interindividual variability, the difference in response between the two eyes of a given individual is negligible. We interpret this finding to mean that as a localizing test in Horner's syndrome, hydroxyamphetamine mydriasis should be useful, because the interindividual variability does not influence the localizing value within an individual.

Neither the age nor the iris color of the subject appeared to influence the amount of mydriasis to 1% hydroxyamphetamine in our subjects. Smith and Smith,[15] however, reported that the pupils of elderly subjects dilate slightly more with 0.5% hydroxyamphetamine than those of younger subjects. One way of reconciling this difference is to consider that the increase in permeability of an aging cornea may cause a higher effective concentration of the
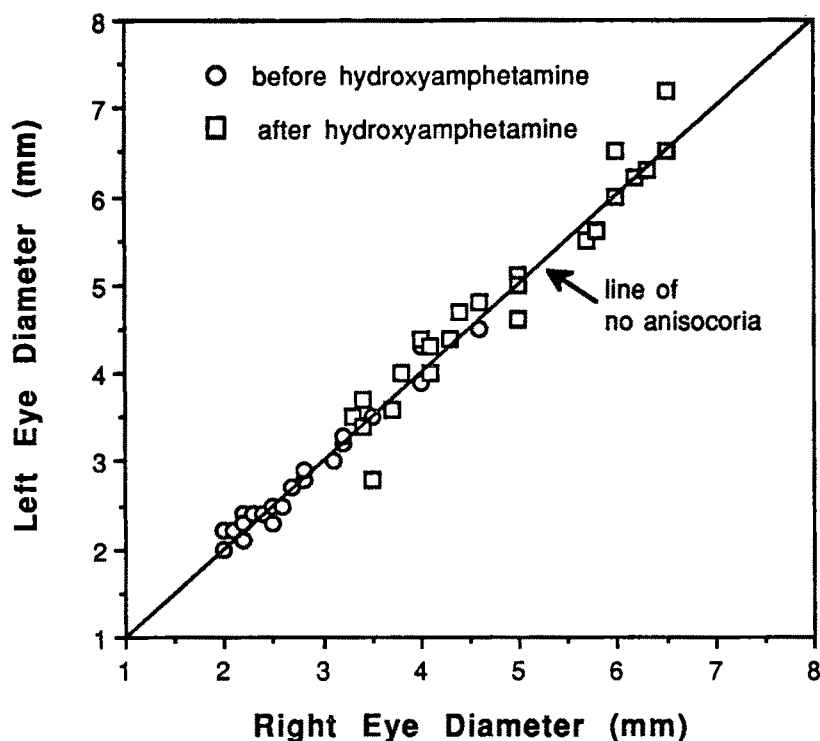
Fig. 3 (Cremer and associates). Effect of hydroxyamp̂hetamine on pupil diameter in normal eyes. Plot of right eye diameter vs left eye diameter for 26 normal subjects, before (circles) and after hydroxyamphetamine (squares). The right and left pupils are of nearly equal diameter, as shown by the close proximity of the points to the diagonal line of equality. Any deviation from this line represents an anisocoria. Hydroxyamphetamine generally does not produce anisocoria in normal subjects because the postdrop points are no further from the line of equality than the predrop points.

drug at the nerve ending whenever a submaximal concentration of hydroxyamphetamine is given topically. The 0.5% solution used by Smith and Smith[15] may not have been strong enough to release all of the norepinephrine stores from the nerve endings. This was suggested by Mensher,[16] who photographed the pupils of 20 normal volunteers (Fig. 4), and it

was later discussed by Gillum.[17] Therefore, at submaximal concentrations of topically applied hydroxyamphetamine (0.5%), corneal permeability differences among age groups may influence the mydriatic effect. At higher concentrations of the drug (that is, two drops of 1.0%), however, mydriasis does not appear to differ as a function of age.

Anisocoria (mm)
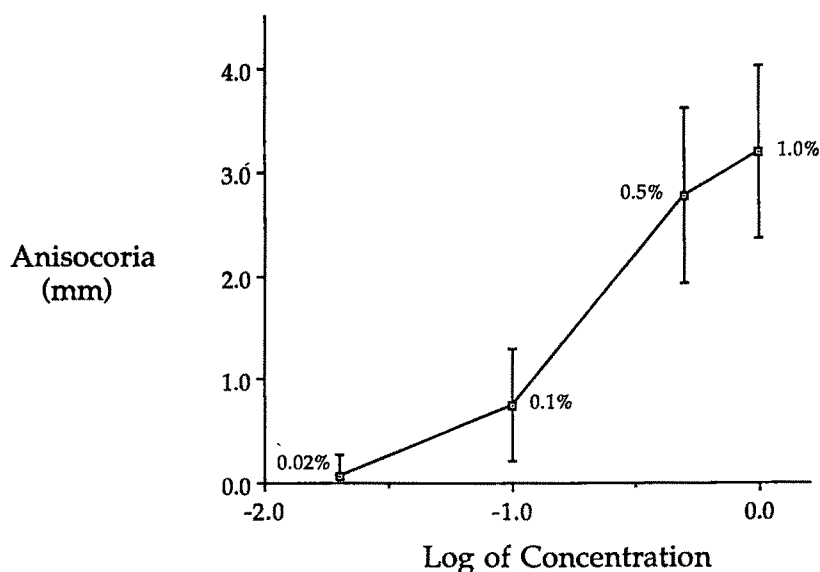
Fig. 4 (Cremer and associates). Hydroxyamphetamine hydrobromide dose response curve. Note that the 0.5% concentration does not always produce full mydriasis. Data from 20 normal volunteers who ranged in age from 4 to 51 years are included. Life-size, self-developing photographs were taken before and 60 minutes after instilling hydroxyamphetamine 1% in the right eye only. The same 20 subjects were retested at least seven days later under identical conditions but with different concentrations of hydroxyamphetamine.

The interocular difference in hydroxyamphetamine mydriasis might be expected to vary in an individual daily. Day-to-day variation, however, should be part of the overall variability. Presumably, some of our subjects were examined on days when they dilated more than usual, and some on days when they dilated less than usual. Because the hydroxyamphetamine test is not used to follow the progression of a sympathetic deficit in a given patient, and is a one-time test for localization, the daily variation in the test within a given individual is not likely to have clinical significance.

Because there is relatively little interocular variability in hydroxyamphetamine mydriasis in a normal individual, a mydriatic difference between the two eyes of a patient with Horner's syndrome is more likely to reflect differences in the number of existing postganglionic neurons than any right eye to left eye variability of the drug's effect.

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Hydroxyamphetamine Mydriasis in Horner's Syndrome

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We studied hydroxyamphetamine hydrobromide 1% (Paredrine) mydriasis in 54 patients with Horner's syndrome to determine its effectiveness in distinguishing preganglionic lesions from postganglionic lesions. The difference in pupillary dilation between the unaffected and affected sides was used as a measure of the hydroxyamphetamine effect. We found that patients who had clinical evidence of damage to the postganglionic neuron of the oculosympathetic pathway had less pupillary dilation on the affected side. In contrast, almost all patients judged to have clinical evidence of preganglionic lesions dilated more on the affected side. We determined the probability that a given difference in pupillary dilation between the involved and uninvolved side is the result of a postganglionic lesion.

THE USE OF hydroxyamphetamine hydrobromide 1% (Paredrine) as a diagnostic test for localizing the site of the lesion in Horner's syndrome was suggested in 1971 by Thompson and Mensher.[1] They showed that when the lesion appeared to be in the postganglionic neuron, the denervated iris dilator muscle responded less to the drug. This fits the known mechanism of action of the drug: hydroxyamphetamine releases the stores of norepinephrine from the postganglionic adrenergic nerve endings at the dilator muscle of the pupil. The postganglionic fibers travel along the internal carotid artery from the superior cervical ganglion to the cavernous sinus, and through the orbit and into the globe. If the postganglionic neuron is dead, there will be no norepinephrine stores to be released, and hence no mydriasis.

There has been some debate about the value of hydroxyamphetamine mydriasis as a localizing sign in Horner's syndrome. Miller,[2] analyzing the data of Maloney, Younge, and Moyer,[3] found hydroxyamphetamine to have a sensitivity of 96% in identifying postganglionic lesions, whereas van der Wiel and van Gijn[4] found the sensitivity to be closer to 40%. Van der Wiel and van Gijn quantified hydroxyamphetamine mydriasis and attempted to define a cutoff point for judging whether the lesion was in the postganglionic neuron.

We undertook to re-examine how much difference in hydroxyamphetamine mydriasis between the two eyes is necessary to determine that the location of the sympathetic deficit is postganglionic. We first studied the variability of hydroxyamphetamine mydriasis in normal subjects.[5] In the present study, we examined hydroxyamphetamine mydriasis in 54 patients with Horner's syndrome.

Subjects and Methods

We obtained the charts of 142 patients in whom Horner's syndrome was diagnosed. The diagnoses were confirmed both by dilation lag of the smaller pupil and by the cocaine test. Five patients with congenital Horner's syndrome were eliminated from the study because they had impaired hydroxyamphetamine mydriasis, presumably because of transsynaptic dysgenesis of the final neuron.[6] The records of the remaining 137 patients with central (first-order neuron damage), preganglionic (second-order neuron damage), or postganglionic (third-order neuron damage) Horner's syndrome were reviewed. In 54 of these patients, the location of the lesion was identified with

reasonable certainty on clinical grounds alone by one of us (H.S.T.), without knowing the results of hydroxyamphetamine testing. Patients with neurologic signs that suggested a central lesion were included in the nonpostganglionic group. Of the 54 patients in whom the disease could be localized clinically, 24 were believed to have nonpostganglionic lesions and 30 were believed to have postganglionic lesions.

The disease could be localized clinically in 54 patients. Twenty-four patients were believed to have nonpostganglionic lesions in which the oculosympathetic pathway was clearly in the chest. Three patients with clear signs of brainstem damage were included in this group of 24, because the damage seemed likely to be proximal to the superior cervical ganglion with nothing to suggest damage to the postganglionic neuron. Thirty patients were believed to have postganglionic lesions in which the damage to the oculosympathetic pathway was clearly along the internal carotid artery. Included in these patients were one patient with an isolated basal skull fracture, one patient with a dissecting aneurysm of the internal carotid artery, and a series of patients with typical cluster headaches. There was nothing to suggest a location other than the postganglionic neuron. In 44 patients, the damage might have affected both the preganglionic and postganglionic neurons, and in some patients no cause for Horner's syndrome could be found.

Many of the patients we excluded from this study had a response to hydroxyamphetamine that appeared to indicate a postganglionic lesion because the pupil on the side of the Horner's syndrome did not dilate, whereas the unaffected pupil dilated substantially. These patients were excluded because the clinical evidence for localization was ambiguous.

The hydroxyamphetamine test was performed in the same way in all of our patients. One drop of hydroxyamphetamine hydrobromide 1% (Paredrine) was instilled into the conjunctival sac of both eyes of each patient. Both eyes were wiped, and 20 to 40 seconds later, a second drop was put in each eye in an effort to balance the dose in the two eyes. Photographs were taken immediately before the eyedrops were administered and 45 to 60 minutes later. The photographs were taken with a C-U 5 Polaroid camera in clinic light (about 25 to 30 foot-candles). Life-size photographs (1:1 magnification) of both eyes were produced so that the pupil diameters could be measured directly

from the photographs with a magnifying ruler to the nearest tenth of a millimeter.

We compared the amount of mydriasis in the normal eye with the mydriasis in the sympathectomized eye; we measured not the final size of the pupil, but how much it had dilated. This difference in dilation between the two eyes was considered positive if the anisocoria increased, and negative if the anisocoria diminished or if the Horner's pupil dilated more than the normal pupil. Thus, a postganglionic lesion would be expected to produce a positive difference in dilation and a central or preganglionic lesion would be expected to produce no difference or a negative difference in dilation.[1] This measurement takes into account any pre-existing anisocoria and therefore is a measure of the difference in the drug-induced mydriasis in the two eyes. Additionally, any difference in psychosensory dilation of the pupils in the before and after photographs will not bias the results because this kind of transient mydriasis affects both eyes.

A logistic regression analysis[7] of our data was used to determine the probability (± 95% confidence limits) that a lesion was postganglionic for a given difference in dilation. The reliability of the regression analysis, based on our sample, was examined by calculating the probability of a postganglionic–nonpostganglionic pair being correctly ranked (that is, the area under the corresponding receiver-operator curve), with the standard error calculated according to Hanley and McNeil.[8]

Results

The actual distributions of difference in dilation for our postganglionic and nonpostganglionic groups are shown in Figure 1. The division between the postganglionic and nonpostganglionic groups was not absolute; however, zero difference in dilation best distinguished the postganglionic and nonpostganglionic groups. With the dividing line in this location, a positive difference in dilation correctly identified the lesion as postganglionic in 88% of the cases (positive predictive value = 88%), and a known postganglionic lesion showed a positive difference in dilation 93% of the time (sensitivity = 93%). When the lesion was judged to be preganglionic or central (nonpostganglionic), the difference in dilation was negative or zero 83% of the time (specificity = 83%). When the differ-
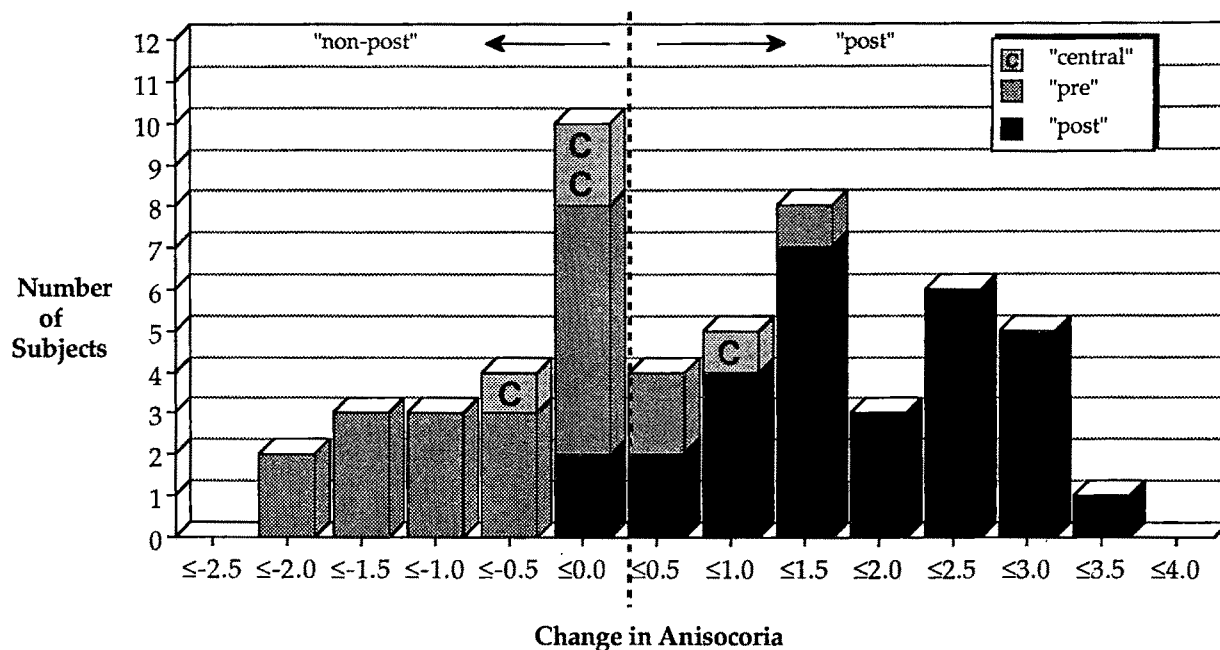
Fig. 1 (Cremer and associates). Histogram shows the amount of difference in dilation induced by instilling hydroxyamphetamine drops in both eyes of 54 patients with Horner's syndrome. The apparent location of the damage to the sympathetic pathway, as judged clinically before the test, is indicated by the shading of the bars. A positive difference in dilation suggests a postganglionic lesion, and no difference or a negative difference suggests a nonpostganglionic lesion. The four patients believed to have central lesions were included in our nonpostganglionic group and are identified with a "C."

ence was negative or zero, the lesion was non-postganglionic 90% of the time (negative predictive value = 90%).

A dividing line like this does not, however,

convey all of the information. The clinician would like to know the likelihood that a patient with a given dilation difference has a postganglionic lesion. The results of the logistic regres-
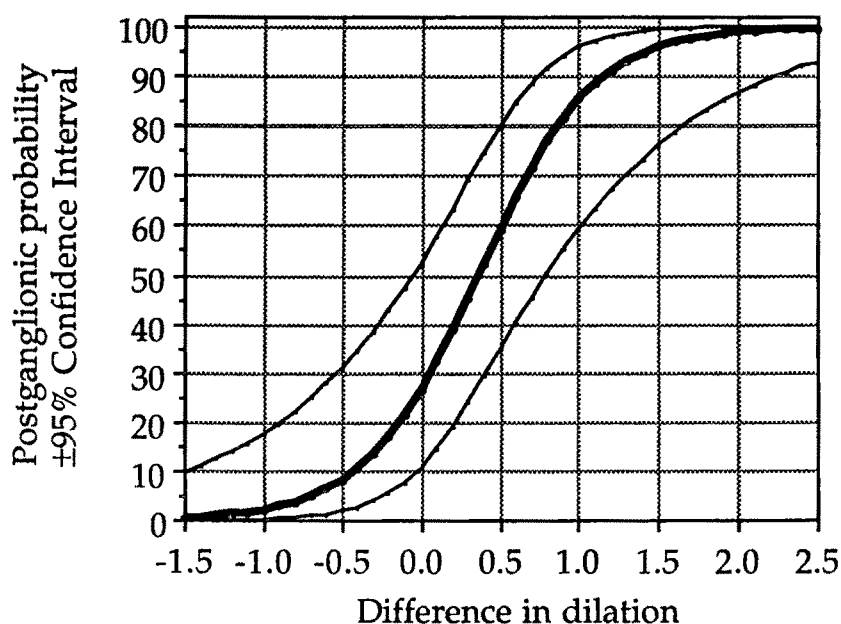
Fig. 2 (Cremer and associates). Postganglionic probability distribution. This distribution shows the probability that a lesion is postganglionic for any measured difference in dilation between −1.5 and 2.5 mm. The dark line indicates the mean probability that the lesion is postganglionic, and the two lighter lines define the 95% confidence interval. For example, the mean probability that a patient with a 1.5-mm difference in dilation has a postganglionic lesion in the oculosympathetic pathway is 96.0% with a lower confidence limit (95%) of 76.2% and an upper limit of 99.4%.

sion analysis (Fig. 2 and the Table) provide this information and can help determine where the lesion is localized.

We also plotted the mydriasis of the affected eye against the mydriasis of the unaffected eye (Fig. 3). Included in Figure 3 are the data obtained from 26 normal subjects.[5] In this graph, the division between postganglionic patients and nonpostganglionic patients can be seen, and the zone occupied by normal responses can be appreciated. A few patients with Horner's syndrome from both groups showed little asymmetry of mydriatic effect from hydroxyamphetamine, and their data overlapped the normative data. Additionally, two patients judged to have nonpostganglionic lesions showed an unexpected positive difference in dilation (Fig. 3). No patient thought to have a postganglionic lesion showed a negative difference in dilation (Fig. 3). Three patients, however, showed symmetric dilation, and one patient showed no hydroxyamphetamine effect in either eye.

Discussion

We have demonstrated that hydroxyamphetamine clearly distinguishes postganglionic from nonpostganglionic cases of Horner's syndrome in most instances. It is clear that in preganglionic and central lesions, the pupil on the affected side usually dilates more in response to hydroxyamphetamine. This could result from an enhanced receptor sensitivity at the dilator muscle, or it may be that the adrenergic nerve endings, untroubled by action potentials in the preganglionic neuron, have accumulated more norepinephrine so that hydroxyamphetamine has a greater effect. This feature—a negative dilation difference in preganglionic lesions—adds to the clinical value of the test.

We have also shown that the hydroxyamphetamine test does not distinguish postganglionic from nonpostganglionic lesions with absolute certainty. There were three postganglionic patients who showed a difference in dilation within the range of variability found in normal subjects, and one patient showed no hydroxyamphetamine effect (Fig. 3). There were also four nonpostganglionic patients who showed a positive difference in dilation, as would be expected for a postganglionic patient. Two of these patients' dilation values fell within the variability seen among normal subjects. The

TABLE

PROBABILITY THAT A LESION IS POSTGANGLIONIC

DIFFERENCE IN DILATION* TO HYDROXY- AMPHETAMINE (MM)	PROBABILITY THAT LESION IS POSTGANGLIONIC	95% CONFIDENCE RANGE	
		LOWER %	UPPER %
−1.5	0.5	0.0	9.6
−1.4	0.7	0.0	10.8
−1.3	1.0	0.1	12.2
−1.2	1.3	0.1	13.8
−1.1	1.6	0.2	15.5
−1.0	2.2	0.2	17.5
−0.9	2.8	0.4	19.6
−0.8	3.7	0.5	22.0
−0.7	4.9	0.8	24.7
−0.6	6.3	1.2	27.6
−0.5	8.2	1.8	30.9
−0.4	10.6	2.6	34.4
−0.3	13.5	3.8	38.3
−0.2	17.1	5.4	42.6
−0.1	21.4	7.7	47.2
0.0	26.5	10.7	52.2
0.1	32.3	14.4	57.6
0.2	38.7	18.8	63.2
0.3	45.5	23.9	69.0
0.4	52.5	29.3	74.0
0.5	59.3	34.8	80.0
0.6	65.9	40.3	84.7
0.7	71.8	45.5	88.6
0.8	77.1	50.5	91.8
0.9	81.7	55.1	94.2
1.0	85.5	59.4	96.0
1.1	88.6	63.3	97.2
1.2	91.2	67.0	98.1
1.3	93.2	70.3	98.7
1.4	94.8	73.4	99.2
1.5	96.0	76.2	99.4
1.6	96.9	78.7	99.6
1.7	97.7	81.0	99.8
1.8	98.2	83.1	99.8
1.9	98.7	85.0	99.9
2.0	99.0	86.7	99.9
2.1	99.2	88.2	100.0
2.2	99.4	89.5	100.0
2.3	99.6	90.7	100.0
2.4	99.7	91.8	100.0
2.5	99.7	92.8	100.0

*Difference in dilation is calculated as the change in diameter of the unaffected pupil minus the change in diameter of the affected pupil.

overlapping cases seen in Figures 1 and 3 can be explained without compromising our hypothe-

Dilation (mm) of affected eye (Horner's)
Dilation of right eye (normal subjects)
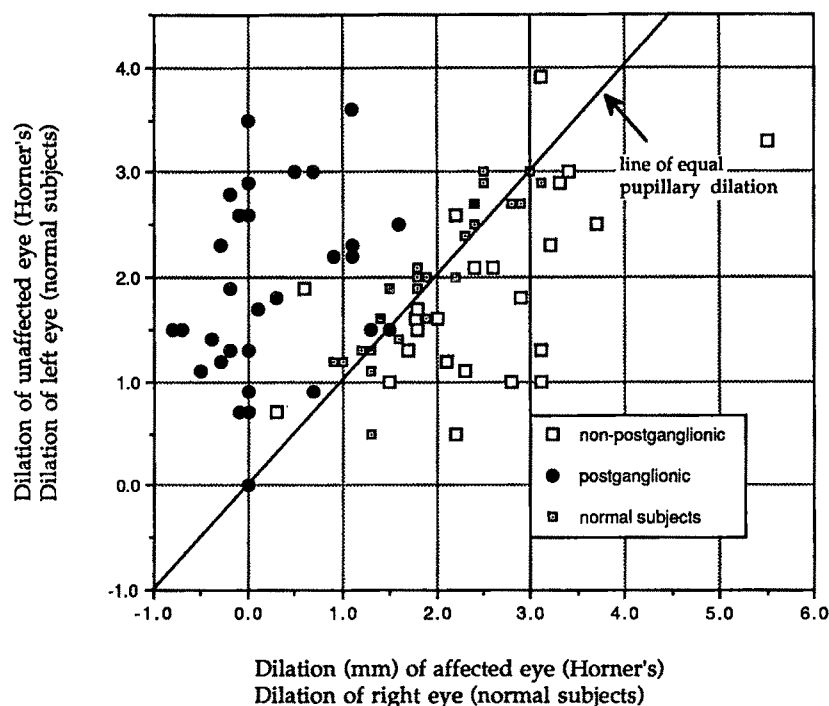
Fig. 3 (Cremer and associates). Comparison of mydriasis. For normal subjects, the x-axis represents the dilation of the right eye and the y-axis represents the dilation of the left eye. For patients with Horner's syndrome, the x-axis represents the dilation of the affected eye and the y-axis represents the dilation of the normal eye. Although the degree of dilation varies widely between individuals, the two eyes of a given normal individual tended to dilate approximately the same amount, as demonstrated by the close proximity of most of the normal subjects to the line of equal pupillary dilation. The postganglionic and nonpostganglionic groups are well separated in this graph: the points representing patients with a postganglionic lesion tend to lie above the line of equal pupillary dilation, and the points representing patients with a nonpostganglionic lesion generally lie below this line.

sis that postganglionic lesions should show a positive difference in dilation, whereas non-postganglionic lesions should show no difference or a negative difference in dilation.

First, it is possible that our clinical localizations may not have been accurate in all cases. The hydroxyamphetamine test is used, after all, because the lesion is often difficult to localize.

Second, a range of variability of difference in dilation exists, as was shown in normal subjects. Factors that contribute to this variability[5] would also be expected to contribute the same degree of variability to the results in patients with Horner's syndrome. This normal variability may explain a small part of the overlap found.

Third, the extent of the oculosympathetic deficit could influence the discriminating ability of the test. Most lesions in patients with Horner's syndrome seem to be incomplete. Psychosensory dilation is partial, segmental dilation paresis can be seen, and partial mydriasis is common. Patients with only a small sympathetic deficit would not be expected to show much difference in dilation, and this would tend to make the pharmacologic localization less certain.

Fourth, there may be situations in which a lesion might appear clinically to be preganglionic yet actually be postganglionic. Sears, Kier,

and Chavis,[9] working with rabbits, showed that damage to the blood supply of the superior cervical ganglion may result from occlusion of vessels lower in the neck. Therefore a lesion producing preganglionic damage to the cervical sympathetic path might, at the same time, impair the blood supply to the superior cervical ganglion and hence show the poor hydroxyamphetamine mydriasis of a postganglionic Horner's syndrome. Such a lesion would be judged clinically to be preganglionic because of the location of the primary injury, but if the blood supply to the superior cervical ganglion were damaged, the lesion would be pharmacologically localized as postganglionic even though the preganglionic pathway was also severed. These patients would be considered to have a false-positive response to the hydroxyamphetamine test. Transsynaptic degeneration of the postganglionic neuron after preganglionic denervation may also be a mechanism by which a clinically localized preganglionic lesion may appear postganglionic when the hydroxyamphetamine test is performed.

Conversely, as van der Wiel and van Gijn[4] have shown, there is also a group of patients in whom the postganglionic neuron is not actually dead, but is only temporarily not conducting impulses. These patients may have middle ear disease or other transient paracarotid prob-

lems. The stores of norepinephrine in the adrenergic nerve endings are still intact and hydroxyamphetamine will still release the norepinephrine and produce a mydriasis, and a false-negative result will occur.

Van der Wiel and van Gijn[4] conceded that every cluster-headache patient with a Horner's syndrome that persists between clusters may be assumed to have a damaged postganglionic neuron of the sympathetic pathway to the eye. They did not believe that a hydroxyamphetamine test was needed to localize the sympathetic lesion in a patient with typical cluster headaches. This may be true; however, cluster-headache patients with damage to the postganglionic sympathetic neuron need not be excluded for this reason from a study of patients designed to demonstrate the appropriate hydroxyamphetamine responses for various lesions in the sympathetic pathway to the eye. Of our postganglionic patients, 19 of 30 (63%) had cluster headaches.

Van der Wiel and van Gijn[4] also used, as their dividing point, a difference in dilation of +1.0 mm, which is a point obtained from their study of normal subjects. Based on that study, +1.0 mm may well be a dividing point suitable for deciding whether the response to hydroxyamphetamine is normal or abnormal. Hydroxyamphetamine is not, however, ordinarily used to make the diagnosis of Horner's syndrome; it is used in an effort to localize the lesion. The location of Van der Wiel and van Gijn's[4] dividing line, with the smaller number of patients in their study, and the exclusion of patients with cluster headaches, may account for the lower sensitivity and specificity found in their study.

By using logistic regression, we have provided probability data that can be used to determine whether the lesion is postganglionic or nonpostganglionic based on the dilation difference in an individual patient with Horner's syndrome.

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OPHTHALMIC MINIATURE

. . . They always looked surprised. No matter the circumstances . . . . The details were different but the eyes were the same. The intellect believed in death but the animal in man thought it was immortal. The eyes were always glossy with outraged surprise.

Tony Hillerman, The Fly on the Wall
New York, Harper and Row, Harper Paperbacks, 1990, p. 17

A Bisulfite-free Intraocular Epinephrine Solution

James W. Slack, M.D., Henry F. Edelhauser, Ph.D., and Mary J. Helenek

We evaluated a preservative-free, sulfite-free epinephrine solution for potential corneal toxicity, which has been described for sulfite-containing epinephrine solutions. The preservative-free, sulfite-free epinephrine solution did not exhibit endothelial toxicity in three-hour paired human corneal endothelial perfusion at two and four times the concentration of the 1:1,000,000 dilution currently recommended for anterior chamber intraocular irrigating solutions. When epinephrine at a dilution of 1:1,000 was injected directly into the anterior chamber of New Zealand white rabbits, there was markedly less corneal edema induced than there was in previous studies with sulfite-containing solutions of comparably low pH but higher buffer capacities. Although potential toxicity exists for any irrigating solution with a pH outside of the 6.5 to 8.5 pH range, the endothelial toxicity of this solution has been reduced by its low buffer capacity, lack of preservatives, and lack of sulfite, offering an extra margin of safety for intraocular use.

DILUTIONS of commercially prepared epinephrine solutions are commonly used intracamerally during anterior segment surgery for control of pupillary dilation and anterior segment hemostasis. Reports of corneal edema after the administration of intraocular epinephrine led to studies of the effects of commercially available epinephrine preparations on the corneal endothelium.[1,2] The toxicity of 1:1,000 and 1:10,000 solutions formulated for intravascular or intracardiac use was determined to be attributable to the presence of sodium bisulfite (a preservative and antioxidant) and a nonphysiologic citrate buffer with a high buffer capacity and an acidic pH of 3 to 4.[3] Epinephrine products labeled as having no preservatives may still contain sodium bisulfite that the manufacturer regards as an antioxidant.[2]

A preservative-free, sulfite-free epinephrine 1:1,000 sterile solution for injection (American Regent Laboratories, Shirley, New York) was recently introduced primarily to avoid potential allergic reactions in the corticosteroid-dependent asthmatic population in which sulfite sensitivity can reach 8.4%.[4] The purpose of this study was to determine the potential corneal toxicity of the preservative-free, sulfite-free epinephrine solution by in vitro paired human cornea endothelial perfusion and after anterior chamber injection in rabbits.

Material and Methods

Paired human eyes were obtained from the Wisconsin Lions Eye Bank. For the ten pairs of human eyes used in this study, the mean donor age (± S.E.M.) was 73.6 ± 1.6 years; the time from death to enucleation was 2.3 ± 0.2 hours; and the time from enucleation to experiment was 12.5 ± 1.0 hours. The eyes were transported and stored in moist chambers at 4 C before experimentation.

The corneas were excised and mounted in a dual-chambered perfusion specular microscope.[5] Both corneas of a matched pair were initially perfused with BSS Plus for a one-hour stabilization period. After one hour, one cornea of the pair was perfused at a rate of 6 ml/hr with either 1:500,000 or 1:250,000 preservative-free, sulfite-free epinephrine (American Regent Laboratories) whereas the other cornea was perfused with BSS Plus for an additional three hours. The resultant epinephrine concentrations were two and four times greater than

would normally be used at the presently recommended 1:1,000,000 dilution.[3] All perfusions were performed at 37 C with a perfusion pressure of 15 to 20 mm Hg. Corneal thickness was measured at 15-minute intervals, and swelling rates were calculated by linear regression analysis.

New Zealand white rabbits weighing approximately 2 kg were anesthetized with intramuscular ketamine HCl (30 mg/kg of body weight) and xylazine (4 mg/kg of body weight). Two drops of proparacaine HCl 0.5% were topically instilled on each cornea. To simulate the most severe case for endothelial toxicity, an eyelid speculum was inserted and a 30-gauge needle on a 1-ml syringe was used to aspirate 0.2 ml of aqueous. The aqueous was aspirated through a shelved limbal stab incision either before or simultaneous with the injection of 0.2 ml of the undiluted 1:1,000 preservative-free, sulfite-free epinephrine through a separate shelved 30-gauge needle stab incision. As a control, the same procedure was performed in the fellow eye of each rabbit, but BSS was injected. Before the injection and ½, one, two, four, six, and 24 hours after the injection, the corneal thickness was measured in each eye by using ultrasonic pachymetry under topical anesthesia with 0.5% proparacaine. After the 24-hour measurement, the rabbits were killed and the corneas were prepared for electron microscopy.

At the end of each experiment, the human and rabbit corneas were fixed in 2.7% glutaraldehyde in phosphate buffer (pH 7.2). The corneas were cut in half and postfixed in 2% osmium tetroxide for two hours. Small pieces of

TABLE
COMPARISON OF BUFFERING CAPACITIES*

ADDITION OF 0.1N NaOH, (μL)	PH		
	AMERICAN REGENT (LOT 9024)	PARKE-DAVIS (LOT 02358)	ELKINS-SINN (LOT 038108)
Initial pH	3.27	3.29	3.27
10	3.55	3.47	3.46
20	4.34	3.84	3.79
30	7.06	4.66	4.55
40	7.55	5.35	5.29
200		6.98	6.81
210		7.03	6.86
220			6.91
230			6.97
240			7.01

*Measurements for buffering capacity of NaOH between 50 and 190 μl were unvaried.

cornea were embedded in low-viscosity epoxy medium, thin sectioned, stained with uranyl acetate and lead citrate, and viewed by using transmission electron microscopy. The other half of each cornea was prepared for scanning electron microscopy by using a modification of the method of Cleveland and Schneider.[6] The corneal halves were penetrated with low-viscosity resin, polymerized overnight at 60 C, glued to stubs, sputter-coated with gold-palladium, and viewed with a scanning electron microscope.

A buffer capacity comparison was performed by pooling ten samples of epinephrine 1:1,000
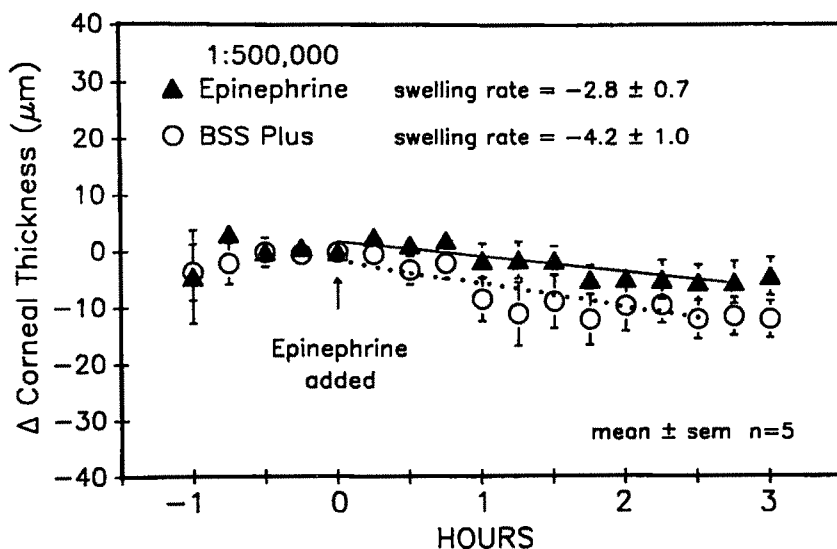
Fig. 1 (Slack, Edelhauser, and Helenek). Corneal swelling (mean ± S.E.M.) of human corneas perfused for three hours in epinephrine 1:500,000 (−2.8 ± 0.7 μm/hr, solid line) and BSS Plus (−4.2 ± 1.0 μm/hr, dotted line) were not significantly different (N = 5).
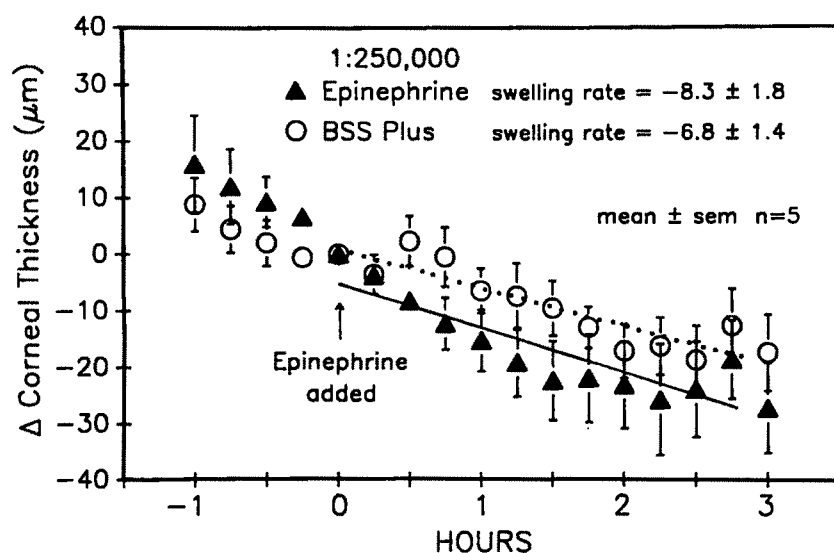
Fig. 2 (Slack, Edelhauser, and Helenek). Corneal swelling (mean ± S.E.M.) of human corneas perfused for three hours in epinephrine 1:250,000 (−8.3 ± 1.8 μm/hr, solid line) and BSS Plus (−6.8 ±11.4 μm/hr, dotted line) were not significantly different (N = 5).

solution (American Regent, Elkins-Sinn, Inc., Cherry Hill, New Jersey, and Parke-Davis, Morris Plains, New Jersey). The pH was measured initially and after serial additions of 0.1N NaOH (Table).

The unpaired t-test was used to compare swelling rates between groups of paired perfused corneas.

Results

The human corneas perfused with 1:500,000 epinephrine for three hours deturgesced at a

rate (± S.E.M.) of −2.8 ± 0.7 μm/hr, which did not significantly differ from the rate of the paired corneas perfused in BSS Plus (−4.2 ± 1.0 μm/hr) (Fig. 1). Similarly, the corneas perfused in 1:250,000 epinephrine deturgesced at a rate of −8.3 ± 1.8 μm/hr, which did not significantly differ from the rate of the paired corneas perfused in BSS Plus (−6.8 ± 1.4 μm/ hr) (Fig. 2).

Electron microscopy of the corneal endothelium after three-hour perfusions with 1:500,000 and 1:250,000 epinephrine solutions disclosed intact intercellular junctions and normal-appearing organelles as in the paired control groups (Figs. 3 and 4).
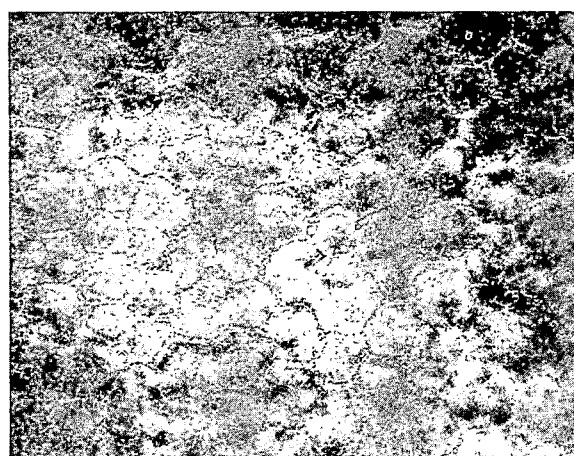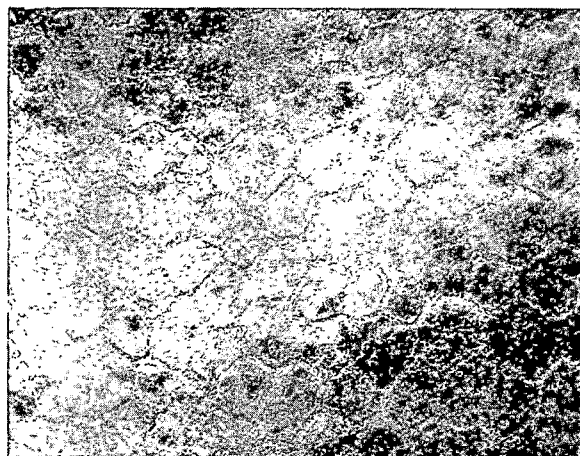
Fig. 3 (Slack, Edelhauser, and Helenek). Scanning electron micrograph of the endothelium of a human cornea perfused with epinephrine 1:250,000 (left) and the control cornea perfused with BSS Plus (right). The posterior surface of the cells is flat, and the normal mosaic pattern is maintained (×500).
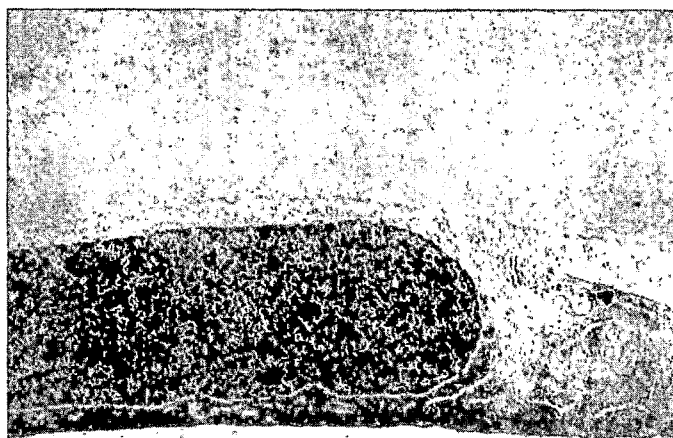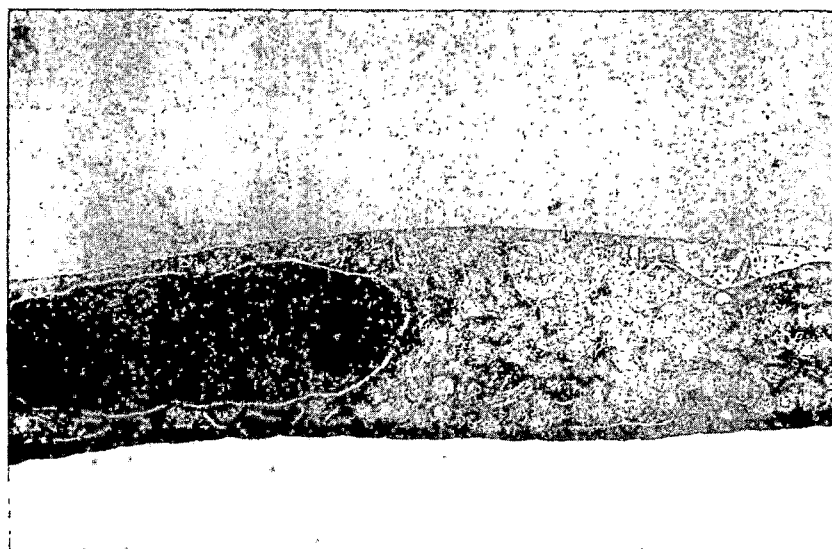
Fig. 4 (Slack, Edelhauser, and Helenek). Transmission electron micrograph of a human endothelial cell perfused with epinephrine 1:250,000 (top) and the control cornea perfused with BSS Plus (bottom). Normal ultrastructural integrity is maintained (× 6,000).
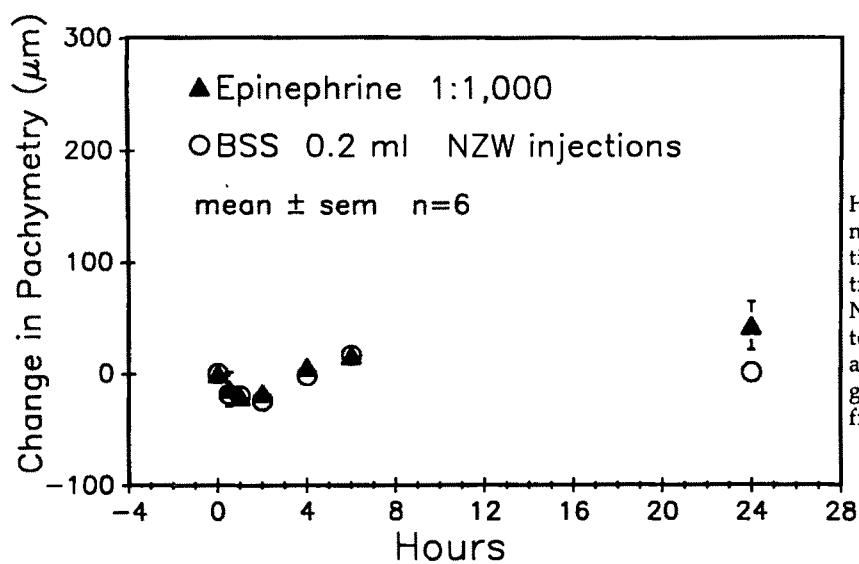
Fig. 5 (Slack, Edelhauser, and Helenek). Change in corneal thickness after anterior chamber injections of epinephrine 1:1,000 (solid triangle) and BSS (open circle) in New Zealand white rabbits. The t-test disclosed that the small increase after 24 hours in the epinephrine group was not significantly different from that of the control group.
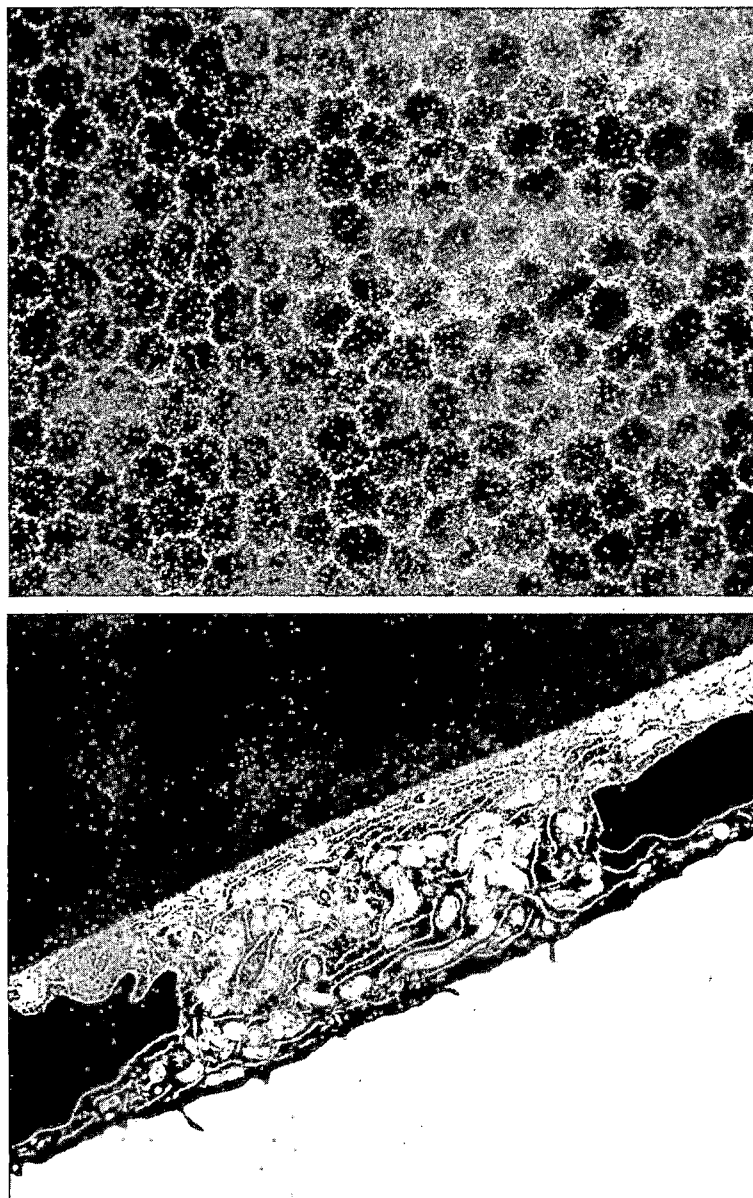
Fig. 6 (Slack, Edelhauser, and Helenek). Scanning electron micrograph (top, × 500) and transmission electron micrograph (bottom, × 5,000) of the endothelium of a rabbit cornea enucleated 24 hours after intraocular injection with epinephrine 1:1,000. Except for the formation of slight openings of the tight junctional complexes which were also present on control eyes, the normal mosaic pattern and ultrastructural integrity are maintained.

Anterior chamber injections of 0.2 ml of the undiluted 1:1,000 preservative-free, sulfite-free epinephrine in rabbits resulted in a small increase in corneal thickness after 24 hours that was not significantly different from that of control eyes injected with BSS (Fig. 5). Electron microscopy showed maintenance of the structural integrity of rabbit endothelial cells except for the slight openings of the tight junctional complexes between cells in both groups (Fig. 6).

A comparison of buffering capacities (Table) showed that the buffering capacity of the American Regent product was only 12% to 15% of that of the Parke-Davis or Elkins-Sinn epinephrine.

Discussion

The preservative-free, sulfite-free epinephrine did not exhibit significant endothelial toxicity in three-hour paired human corneal perfusions at two and four times the concentration of the 1:1,000,000 dilution that is commonly recommended for anterior segment irrigating solu-

tions. Swelling rates were not significantly different from the paired control eyes perfused in BSS Plus, and electron microscopy disclosed that normal ultrastructural integrity was maintained.

When epinephrine 1:1,000 was injected undiluted into the anterior chamber of New Zealand white rabbits, there was no significant increase in corneal thickness or endothelial ultrastructural changes compared to control eyes. In a previous study[2] corneal thicknesses increased over 400 μm after the injection of sulfite-containing epinephrine solutions or acidified saline solution with a high buffer capacity with associated loss of endothelial structural integrity. The lack of significant corneal edema or endothelial toxicity in the present study is consistent with the low buffer capacity of the preservative-free, sulfite-free epinephrine solution.

We still recommend that 0.5 ml of 1:1,000 epinephrine be added to 500 ml of BSS Plus for a final dilution of 1:1,000,000 even if the preservative-free, sulfite-free epinephrine is used. In rare instances, when a more concentrated solution is necessary, 1 ml of 1:1,000 epinephrine may be added to 30 ml of BSS Plus (1:30,000), and 0.2 ml of this mixture is injected into the anterior chamber.[3] Plasma concentrations of adrenaline and noradrenaline do not rise significantly after intraocular irrigation with a solution of epinephrine 1:500,000.[7] With the use of more concentrated solutions and preoperative phenylephrine for dilation, however, ocular surgical personnel should remain alert for signs of potential systemic epinephrine toxicity (such as headache, palpitations, tachycardia, or increased blood pressure).

Although potential endothelial toxicity exists for any irrigating solution with a pH outside of the 6.5 to 8.5 pH range,[8,9] the endothelial toxicity of this solution has been reduced by its low buffer capacity, lack of preservatives, and lack of sulfite, offering an extra margin of safety for intraocular use.

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EDITORIAL

Ophthalmology and Specialty Education for Medical Students

Herbert E. Kaufman and Janine Edwards

In the past, the teaching of specialty medicine has been a source of great anguish and sometimes capricious action by curriculum committees. Some believe that students should have some exposure to the specialties, and specialists strongly agree. Conversely, others believe that the medical student curriculum is already too crowded. The time scheduled for clinical specialties devours the larger blocks of time necessary for in-depth general courses and the development of interpersonal skills, history taking, role modeling in medicine, and self-education by the student.[1] In some schools, specialty teaching has been relegated to elective experiences. In others, specialty clerkships involve tagging after residents or staff. Sometimes the appropriation of curriculum time has been an exercise in departmental political power rather than a rational design fitted to the needs of the medical students.

"Highly specialized medical faculty members all too often do not clearly specify the knowledge, skills, values, and attitudes that students should acquire during their clinical education .... The lack of consensus (in specific terms about what students should accomplish) is frequently compounded by failure to differentiate between the clinical knowledge and skills essential for all physicians and those necessary for the specialized education of residents and fellows."[2]

Our purpose is not to solve all of these problems but rather to suggest an approach to the teaching of specialty medicine that may improve the students' essential core knowledge, diagnostic skills, and ultimate performance as physicians.

The General Premise—There are two separate types of clinical learning in which medical students must engage: the transfer of skills and information and their personal development as physicians. Successful transfer of skills and information requires that each of the specialties of medicine and surgery impart to students a

knowledge of diagnostic skills as well as of the most important manifestations and treatments in that specialty. Student self-education should be encouraged, but the curriculum presented must include the examination and treatment techniques that students are unlikely to learn for themselves. In ophthalmology, for example, students need to learn how to do a good ophthalmoscopic examination, to check intraocular pressure, to recognize retinal manifestations of diabetes and strabismus, to treat acute trauma, and to learn in detail what failure to treat these conditions will ultimately do to vision. Similarly, in otorhinolaryngology, students must learn to do good ear, nose, and throat examinations, to examine babies for deafness, to recognize labial and laryngeal cancers, and to treat these and other diseases. In neurology, students need to learn how to do a neurologic examination and obtain some knowledge of stroke and the major degenerative diseases. Much of this must be taught in a small group format that permits skill practice.

In addition to the transfer of specific skills and information, students must have the opportunity for personal development as physicians. They must practice diagnostic skills, draw conclusions about therapy, and have their conclusions validated. They must interact under supervision with patients to develop clinical and humanistic values and attitudes.

Corollary 1—There are essential diagnostic techniques and skills, as well as specific areas of information, that are best taught to each student as part of a specialty rotation. Omitting these topics seriously handicaps the physician.

Corollary 2—The curriculum used to teach diagnostic techniques and essential information in each specialty must be specifically designed for the medical student and will probably require intensive small group instruction and practice. This teaching may not bear any particular relevance to what a specialist in the field actually does most of the day.

Thus, an ophthalmologist may devote much study to refraction, cataract extraction, the repair of retinal detachments, or the performance of corneal transplants, but these techniques are of little importance to medical students. Medical students require a specific and efficiently taught curriculum tailored to the education of the general physician. When students simply follow an ophthalmologist through a clinical day, the bulk of the time is spent on irrelevant information and diagnostic techniques. The

specialist cannot be permitted to waste the students' time in such a manner. The transfer of information and skills must be worked out by each specialty in a way that is most efficient for the student. The common practice of specialty education by personal apprenticeship is not only inefficient, but indefensible in terms of medical education, except for those students who wish to partake of the emotional experience of what a particular specialty is really like. An elective clerkship can fulfill that function.

Corollary 3—For students to mature as physicians, they must act like physicians repeatedly, over a significant period of time. We believe that this is a developmental experience and is different from that of information and skills transfer. During this developmental stage, students learn to take complete histories, do physical examinations, develop diagnostic skills, and make therapeutic decisions (which may or may not be implemented). Indeed, students learn to be physicians by acting out the role of a physician, often seeking role models and developing patterns of learning from and caring for patients.

Relating to patients, gathering a data base (including reference work), formulating a differential diagnosis, and suggesting therapy require personal development over a long period of time. Clinical clerkships provide the broad and deep immersion necessary for this development.

This type of experience is probably necessary in at least one medical and one surgical specialty. It may also be necessary in pediatrics. Whether it is actually necessary in other specialties such as obstetrics and psychiatry is arguable, but it is almost certainly unnecessary in all of the specialties of medicine and surgery.

Given this premise, the logical conclusions are that specialties must be represented in the medical school curriculum, but that each specialty has an obligation to define the goals and objectives of its limited curricular time in terms of the diagnostic techniques and knowledge required by the general physician. This information is not efficiently taught by assigning a student to spend time in a specialty clinic, but rather requires a conceptual reorganization and a specifically designed teaching program. In ophthalmology, the problem of the core curriculum was addressed by asking general physicians, specialists in internal medicine, and pediatricians what they believe a general physician most needs to learn about ophthal-

mology. From this information, a curriculum was specifically designed for the medical student rather than for the specialist.[3]

Such an approach could well serve other specialty areas of medicine. Requiring in-depth exposure to each specialty for every student cannot be justified. Essential knowledge of diagnostic techniques can be taught in relatively small blocks of time, once it is decided to stress the material that is indispensable to the general physician. With this approach, it may be possible not only to provide a comprehensive education in the specialized diagnostic techniques and diseases that the general physician needs, but also to structure the curriculum to permit more time for in-depth clinical experience.

If the educational contribution of the medical and surgical specialties, the core curriculum, is clearly defined in terms of the general education of the physician, it can be taught with far greater effectiveness than is now available in most medical schools, and also in less time. To this end, the subspecialties must devise and implement a curriculum especially geared to the students' general education. To be sure, elective time should be made available for gaining an in-depth feeling of what it is like to perform as a particular specialist and what life in that specialty would be like. However, this should be possible within the scope of a general medical school curriculum in which there is a clear separation between the need for the transfer of information and skills and the need for in-depth, personal development experiences.

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LETTERS TO THE JOURNAL

Particles Resembling Retrovirus and Conjunctival Kaposi's Sarcoma

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Fig. 1 (Dugel and associates). Nodular lesion in the bulbar conjunctiva.

The infectivity and mechanisms of pathogenesis of the retroviruses, specifically the human immunodeficiency virus, are under rigorous investigation. These viruses are thought to infect lymphocytes selectively and to induce production of various cytotrophic and cytopathic agents. Nakamura and associates[1] reported that a specific growth factor produced by retrovirus-infected lymphocytes causes proliferation of Kaposi's sarcoma cells in culture. The virus, however, has not been recovered from Kaposi's sarcoma cells and an in vivo confirmation of this trophic effect is lacking.

Three homosexual men were examined for conjunctival Kaposi's sarcoma. All three were known to be HIV-antibody positive. A 4- to 6-mm raised yellow-white nodule was seen in the bulbar conjunctiva in the same eye as the conjunctival Kaposi's sarcoma in all three patients (Fig. 1). No other ocular abnormalities were found. Two patients had diffuse Kaposi's sarcomas of the skin. None of the patients were receiving any treatment.

A biopsy of the yellow-white nodule was performed in all three patients. Light microscopy of the yellow-white nodules showed extensive squamous metaplasia, foci of acanthosis, and elastosis of the subepithelial stroma. Electron microscopy of the ocular surface lesions from all three patients disclosed multiple cytoplasmic inclusions and particles resembling retrovirus in the yellow-white nodules, but not in the Kaposi's sarcoma lesions or in the peripheral conjunctiva. Although aberrant immature particles containing granular matrix were seen in the cytoplasm, the appearance of the budding particles was similar to that reported previously for retroviruses.[2] In general, two types

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Fig. 2 (Dugel and associates). Semicircular- or crescent-shaped budding characteristic of virus particles. Note immature particles along the plasma membrane (× 40,750).

of particles were seen. Crescent-shaped particles with a dense nucleic acid core, characteristic of retroviruses, budded from the plasma membrane (Fig. 2). Additionally, complete, spherical particles measuring 100 nm in diameter were seen in the extracellular space. The core of these particles was not clearly defined, and the typical bar-shaped central nucleoid, characteristic of mature HIV particles, was not seen. Numerous intracytoplasmic particles with a mean diameter of 100 nm were seen within vesicles. Presumably these represent immature forms or particles in various stages of maturation. Inclusion bodies of undefined origin were scattered throughout the cytoplasm.

Human immunodeficiency virus has been isolated from various ocular tissues: tears, conjunctiva, cornea, iris, vitreous, and retina. In all patients, no external lesions or nidus of infection were seen. The conjunctiva was clinically normal. Nakamura and associates[1] have shown that C4+T-lymphocytes infected with human T-lymphotrophic virus type I or II or with HIV type I or II release a growth factor that greatly enhances the growth of Kaposi's sarcoma cells in culture. However, no genomic sequences of any virus have been detected in Kaposi's sarcoma tissue. Although the appearance of these particles is distinct from that of mature retrovirus particles, they may represent immature forms developing within macrophages and monocytes. The absence of similar particles in the adjacent Kaposi's sarcoma and in surrounding conjunctiva suggests that the nidus of the

infection is discrete. The proximity of these lesions to the Kaposi's sarcoma raises the possibility of a cytotrophic effect. A viral infection was not suspected at the time of biopsy, so no attempts were made to isolate a virus; but we are currently collecting material to genetically and biochemically characterize these particles. It is expected that approximately 20% of patients with systemic Kaposi's sarcoma will have ocular involvement.[3] Delineation of the possible role of retroviruses in the growth of Kaposi's sarcoma may provide important information as to the pathogenesis of this increasingly common ocular tumor.

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A Case of Macular Detachment With Three Causative Factors

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Congenital pits of the optic nerve head cause macular detachment in some patients.[1] In idiopathic central serous choroidopathy, the macular detachment is thought to be caused by a detachment or defect of the retinal pigment epithelium. Fluorescein angiography in such a patient demonstrates leakage into the subretinal space from the retinal pigment epithelial defect.[2] Posterior slit tears of the retina in association with optic disk anomalies have also been reported to cause macular detachment.[3] We treated a patient with macular detachment in whom each of these causes was present.

A 51-year-old man had a two-day history of blurred vision and metamorphopsia in the right eye. Best-corrected visual acuity was R.E. 20/40. There was an obvious temporal optic nerve head coloboma (pit) with a macular detachment extending from the temporal disk margin. Two tiny, horizontal slit tears were apparent in the detached retina slightly temporal to the temporal disk margin. Fluorescein angiography also disclosed a leak of the retinal pigment epithelium, typical of idiopathic central serous choroidopathy (Fig. 1). The patient was followed up for six months at which time cystic changes developed in the macula. The leak of the retinal pigment epithelium was then successfully sealed by argon green laser photocoagulation. The serous macular detachment, however, persisted.

Four months later, the patient underwent a pars plana vitrectomy with fluid-gas exchange on the assumption that the persistent macular detachment was because of the optic nerve pit or the slit tears of the retina, or both. Because endolaser photocoagulation was not then available to us, argon green laser photocoagulation was applied postoperatively through the gas bubble. Treatment was applied to the area around the temporal edge of the disk in an attempt to prevent fluid from passing into the subretinal space from the optic pit[4] and to seal the two retinal tears. The gas bubble had displaced the fluid inferiorly, but when the bubble was absorbed the fluid again migrated under the macula and detached it. A second gas injec-
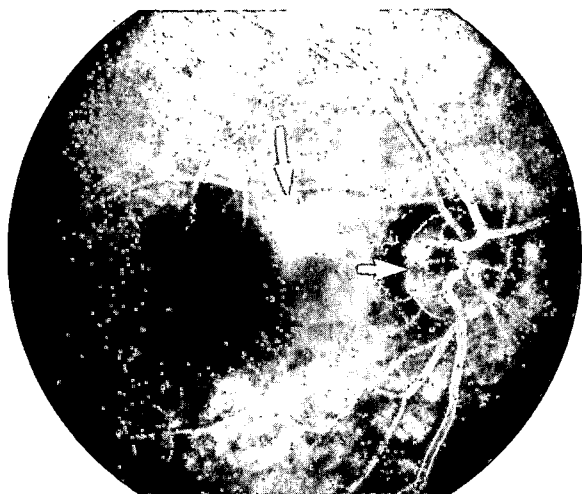
Fig. 1 (Brinkley, Jarus, and Ryan). Late phase fluorescein angiogram showing retinal pigment epithelial leakage (long arrow) and optic nerve head pit (short arrow). The slit tears cannot be visualized.
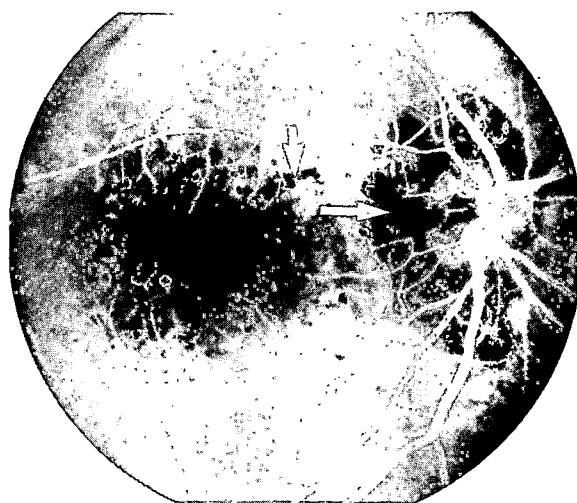
Fig. 2 (Brinkley, Jarus, and Ryan). Arteriovenous phase fluorescein angiogram two years after treatment. The macula is flat. The retinal pigment epithelial leak has been sealed (short arrow) and the area adjacent to the disk on the temporal side (including the slit retinal tears) has been treated (long arrow), each with argon green laser photocoagulation. The small hypofluorescent spots with hyperfluorescent edges are from the krypton grid laser.

tion, followed by a light macular grid treatment with krypton laser, resulted in flattening of the macula. Visual acuity returned to R.E.: 20/20 and the patient has been followed up for four years without recurrence (Fig. 2).

When serous macular detachment occurs in association with an optic pit, fluorescein angiography can rule out other causes of detachment. Once all sources of fluid ingress into the subretinal space have been eliminated; serous subretinal fluid may still remain. In such cases a light grid laser treatment may facilitate retinal flattening, possibly by encouraging repopulation of the retinal pigment epithelium with more metabolically active cells, thereby restoring the outer blood-retinal barrier.[5]

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Acute Posterior Multifocal Pigment Epitheliopathy and Optic Neuritis in a Family

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Acute posterior multifocal pigment placoid epitheliopathy is a chorioretinal inflammatory disease of uncertain origin. Optic neuritis or papillitis has been described in patients with this condition.[1] We reported the association of HLA antigens B7 and DR2 with acute posterior multifocal pigment placoid epitheliopathy.[2] The HLA antigens B7 and DR2 have also been associated with optic neuritis in several studies.[3] We treated a mother and son who developed optic neuritis and a daughter who developed acute posterior multifocal pigment placoid epitheliopathy within a six-month period.

Case 1

The 46-year-old proband had painless central visual loss in the left eye in October 1987. Her vision improved over the next three weeks. She had no other neurologic symptoms and a normal brain magnetic resonance image. Results of an examination at our clinic on March 14, 1988, showed visual acuity of R.E.: 20/20 and L.E.: 20/30. A 0.6-log unit relative afferent pupillary defect was apparent in the left eye. Critical flicker fusion was 25.8 Hz in the right eye and 21.5 Hz in the left eye. Extraocular movements were normal. Goldmann visual fields were normal. Mild temporal disk pallor was present in the left eye. Results of the retinal examination were normal. Resolved optic neuritis was diagnosed.

Case 2

The proband's 24-year-old son had decreased vision in the left eye and headaches in December 1987. He had no other neurologic complaints. Results of an examination in our clinic on March 14, 1988, showed visual acuity of 20/20 in each eye. A 0.3-log unit relative afferent pupillary defect was apparent in the left eye. Critical flicker fusion thresholds were 31.8 Hz in the right eye and 28.4 Hz in the left eye. Extraocular movements were normal. Goldmann visual fields showed a small, nasal, paracentral scotoma in the left eye. The left optic disk was slightly pale. Results of a retinal examination were normal. Mild optic neuritis was diagnosed as the cause of his visual loss in the left eye.

One year later, no further visual or neurologic symptoms had occurred in either patient.

Results of the ophthalmic examination were unchanged and fluorescein angiography was normal.

Case 3

The proband's 29-year-old daughter developed a paracentral scotoma of her left eye in February 1988 several days after having a flu-like illness. Visual acuity was 20/15 in each eye. The anterior segment was normal. Amsler grid testing confirmed a paracentral scotoma of the left eye. Ophthalmoscopy showed multiple deep, yellow-white, placoid lesions in each macula consistent with acute posterior multifocal pigment placoid epitheliopathy.

The follow-up examination in July 1989 showed no visual symptoms. Visual acuity was 20/15 in each eye. There was no relative afferent pupillary defect. Central 10-degree visual fields were normal. A mild patch of retinal pigment epithelial hypertrophy and atrophy was apparent at the site of previous activity. No new lesions were apparent.

All three patients had the HLA antigens B7 and DR2 typical of both acute posterior multifocal pigment placoid epitheliopathy and optic neuritis. The complete HLA antigens and haplotypes were the following: mother, A3, B7, DR2, DQw1; son, A2, A3, B7, B22, DR2, DR6, DQw1; and daughter, A3, B7, DR2, DQw1. It is unlikely that the occurrence of these three conditions in this family was coincidental. Choroidal arteriolar occlusion with overlying retinal pigment epithelial damage has been suggested as the primary site of injury in acute posterior multifocal pigment placoid epitheliopathy.[4] The peripapillary choroid supplies the prelaminar and retrolaminar parts of the optic nerve.[5] Perhaps in these immunogenetically predisposed individuals, inflammation in the peripapillary choroid produced optic neuritis or ischemic optic neuropathy, whereas inflammation of the choroid or retinal pigment epithelium elsewhere caused the creamy-white lesions of acute posterior multifocal pigment placoid epitheliopathy, which hypofluoresce early and stain late.

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Artificially Produced Quadrantanopsia in Computed Visual Field Testing

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A 34-year-old woman was referred to our institution because of high intraocular pressure and bitemporal superior quadrantanopsia on a computed visual screening field. Examination disclosed that she had a left superior homonymous quadrantanopsia on a field analyzer test using the 24-2 strategy (Fig. 1). Confrontation and tangent screen visual fields failed to corroborate this defect. Further neuro-ophthalmologic examination disclosed an 18-month history of occipital headache described as pounding and associated with photophobia and nausea. Although the history might have been compatible with a transient migrainous homonymous field defect, the previous bitemporal defect remained mysterious. Results of the remaining ocular examination were normal, except for intraocular pressure of 22 to 24 mm Hg. The optic disks had 0.3 cup/disk ratios. The nerve fiber layer and magnetic resonance imaging were normal. The patient was referred to her physician for continued follow-up.

We considered the possibility that this patient had nonorganic field loss, but we thought it unlikely that one could produce such a reli-

RIGHT
ACE 34
FIXATION LOSSES 1/18
FALSE POS ERRORS 0/10
FALSE NEG ERRORS 1/7
QUESTIONS ASKED 309
FOVEA: 36 DB
TEST TIME 00:09:47

LEFT
ACE 34
FIXATION LOSSES 0/18
FALSE POS ERRORS 0/7
FALSE NEG ERRORS 0/6
QUESTIONS ASKED 285
FOVEA: 37 DB
TEST TIME 00:08:59
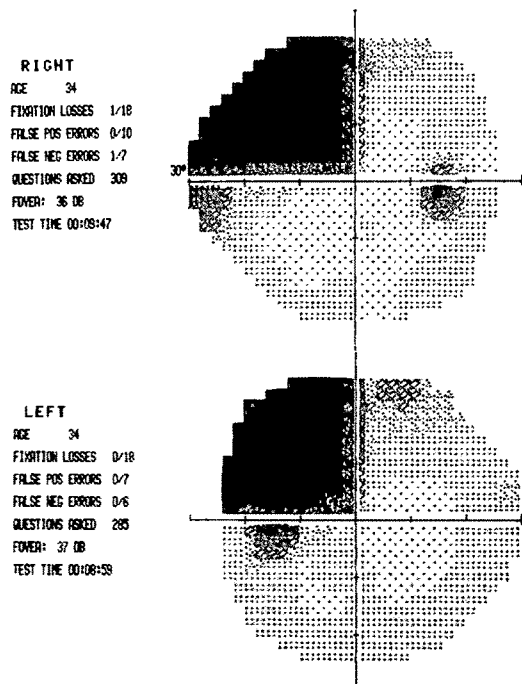
Fig. 1 (Glovinsky and associates). Left superior homonymous quadrantanopsia on the patient's field analyzer 24-2 test. Note the excellent reliability reflected by the minimal number of fixation losses, false-positive errors, and false-negative errors.

able homonymous defect during field analyzer threshold testing. With one of us as the subject, we attempted to create an upper quadrant defect. While the test was running, the subject recognized a successful strategy for creating a defect (Fig. 2). If the subject fails to respond to the light stimulus in the chosen quadrant at the beginning of the test (when light stimuli are directed in four points, one per quadrant), the

RIGHT
ACE 36
FIXATION LOSSES 0/20
FALSE POS ERRORS 0/11
FALSE NEG ERRORS 0/10
QUESTIONS ASKED 342
FOVEA: 37 DB
TEST TIME 00:10:31
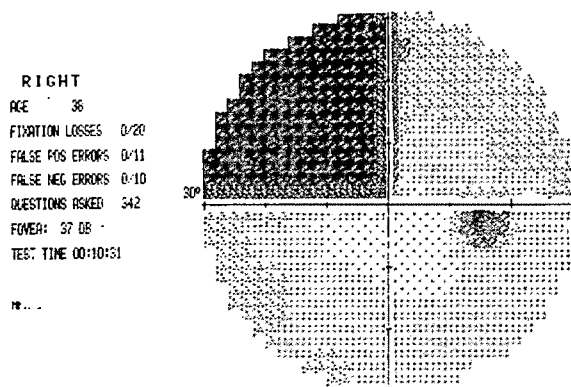
Fig. 2 (Glovinsky and associates). Artificially produced quadrantanopsia in field analyzer test. Note the perfect reliability.

field analyzer directs only bright stimuli in that quadrant. The subject is then aided in not responding in the chosen quadrant, since both position and brightness clues are available.

The reason that only bright stimuli are directed after no response to one of the four cardinal points is a product of the protocol for field analyzer threshold testing. The design attempts to save time in determining threshold by starting near the true threshold. Subsequent testing within each quadrant is based on the initial threshold at the cardinal point measured at the beginning of the test. Once the subject does not respond to a bright light at the first point, the testing at neighboring points always begins with a bright test object as well. (Where threshold is low and sensitivity high, the first presentation for a neighboring point might be much dimmer, that is, closer to the expected low threshold.) Moreover, the total number of stimuli directed in the quadrant with reduced sensitivity are few because the machine will conclude that threshold is 0 after two negative responses to the bright light.

Clinicians should be alert to the possibility of nonorganic quadrantanopsia, hemianopsia, and altitudinal defects in field analyzer testing.

Mumps Neuroretinitis in an Adolescent

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Mumps is a contagious childhood viral infection that had a marked decline in annual incidence between 1967, when the live attenuated mumps vaccine was licensed, and 1985. An increase in the incidence of mumps in adolescents, however, has been recently documented.[1] We treated an adolescent who had neuroretinitis associated with mumps.

A 15-year-old boy had an upper respiratory
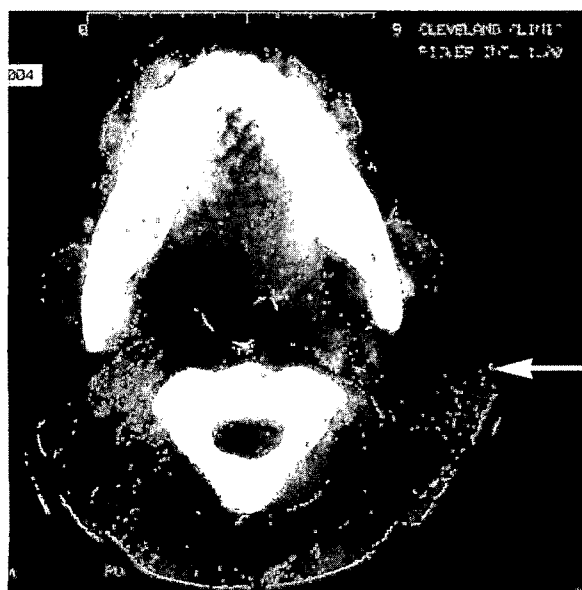
Fig. 1 (Foster and associates). Computed tomographic scan demonstrating an enlarged left parotid gland (arrow) at the level of the body of the mandible.

Fig. 2 (Foster and associates). Fundus photograph of the right eye demonstrating optic nerve head edema and a macular star exudate.

infection in October 1989. During the next two weeks, he developed a severe, persistent, retroorbital headache, fever, and increasing left facial and neck swelling. The patient also noted progressive worsening of vision in the right eye.

A tender and fluctuant 6 × 8-cm preauricular mass on the left extending to the angle of the mandible was found on examination. Computed tomography disclosed an enlarged left parotid gland (Fig. 1). Visual acuity was R.E.: 20/200 and L.E.: 20/20. There was a right relative afferent pupillary defect. Goldmann visual field testing demonstrated a right centrocecal scotoma. No anterior segment inflammation was noted, and intraocular pressure was 15 mm Hg in each eye. Ophthalmoscopy showed marked edema and hyperemia of the optic nerve head, and a macular star exudate in the right eye (Fig. 2). Two small, white intraretinal lesions in the inferior midperipheral retina of the right eye were observed. There was vitreous cellular reaction overlying the optic nerve head and retinal lesions. Cerebrospinal fluid analysis disclosed a lymphocytic pleocytosis, hypoglycorrhachia, and increased protein level.

Two days later, visual acuity had deteriorated to R.E.: 20/400, and the optic nerve head edema was more pronounced. Intravenous therapy with methylprednisolone acetate, 500 mg every

12 hours, was begun. Visual acuity improved during the next two weeks to R.E.: 20/100. The optic nerve head edema decreased, there was less vitreous reaction, and the macular star exudate was more prominent. Serum mumps IgG antibody level was 7.90 and interpreted as high positive, as determined by an enzyme-linked immunosorbent assay. Levels greater than 1.00 are positive. In February 1990, visual acuity was R.E.: 20/40. The relative afferent pupillary defect had resolved, the optic nerve head appeared normal, and two small chorioretinal scars were noted in the inferior peripheral retina at the site of previous inflammation.

Mumps is a communicable viral disease with protean clinical findings that include parotitis, meningitis, deafness, encephalitis, epididymoorchitis, pancreatitis, and rarely myocarditis, nephritis, and thyroiditis.[2] It is also associated with a wide spectrum of ocular inflammation, such as dacryocystitis, optic neuritis, neuroretinitis, keratitis, conjunctivitis, iritis, and scleritis.[3] Our patient had clinical findings consistent with mumps, most notably acute parotitis. He had neuroretinitis with involvement of the optic nerve head and peripapillary and peripheral retina of the right eye. Optic nerve inflammation associated with mumps is usually a complication of a central nervous system infection, and our patient's cerebrospinal fluid studies were compatible with viral meningitis.

A recent report indicated that since 1985, when a record low of 2,982 cases of mumps were reported nationwide, the incidence of mumps has been increasing yearly to a level of 12,848 cases in 1987.[1] This rise has been attributed to the delay between the licensure of the mumps vaccine in 1967 and its routine administration in 1977, which resulted in a relatively underimmunized cohort of adolescents.[1] Vaccine failure may be another reason for the resurgence of mumps. Estimations of mumps vaccination failure range from 10% to 25% of those immunized.[4] Our patient had received his vaccine at 31 months of age and most likely represents a vaccine failure. This case serves to alert ophthalmologists to the increasing incidence of mumps in adolescents, and as a reminder of the associated ocular manifestations such as neuroretinitis.

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Morning Glory Disk Syndrome Associated With Subretinal Neovascular Membrane Formation

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An enlarged, excavated optic nerve head with anomalous retinal vessels originating from deep within the nerve substance and coursing over the edge of the disk has been termed the morning glory syndrome.[1] This disk anomaly is typically unilateral and associated with decreased visual acuity and an afferent pupillary defect, although patients with normal visual acuity have been described.[2] Its clinical significance lies in its association with other ocular abnormalities including nonrhegmatogenous retinal detachment and strabismus, as well as systemic associations including basal encephalocele and hypertelorism.[3] We treated a patient with morning glory disk syndrome who developed a subretinal neovascular membrane originating from the edge of the anomalous disk and extending into the central portion of the macula.

A 23-year-old woman was examined at our institution for decreased visual acuity and metamorphopsia of two months' duration in her right eye. Review of the patient's records disclosed a previously documented visual acuity of R.E.: 20/20 seven years earlier, and previous examinations noted an anomalous optic disk, a 0.6-log unit relative afferent pupillary defect, and an enlarged blind spot. Visual acuity was R.E.: 20/100. The relative afferent pupillary defect was unchanged, and Amsler grid testing showed distortion over central fixation. Ophthalmoscopic examination disclosed a gray, irregular choroidal lesion with overlying subretinal fluid as well as surrounding subretinal hemorrhage, adjacent to an anomalous disk. Fluorescein angiography confirmed a juxtafoveal and subfoveal neovascular complex (Figure). Because of the location of the neovascular membrane, laser photocoagulation was not recommended. The patient's visual acuity stabilized at R.E.: 20/200 two months later.

Morning glory syndrome is an uncommon congenital anomaly of the optic nerve. Previous studies have emphasized an overall poor visual outcome in these patients because of either strabismus or anisometropia resulting in amblyopia, and macular involvement from nonrhegmatogenous retinal detachment.[1,4] In the absence of associated ocular and systemic complications, however, some patients retain good visual acuity.[1]

Our patient had documented, good visual function before developing signs and symptoms of a subretinal neovascular complex. Because subretinal neovascularization is a potentially treatable lesion if discovered in an
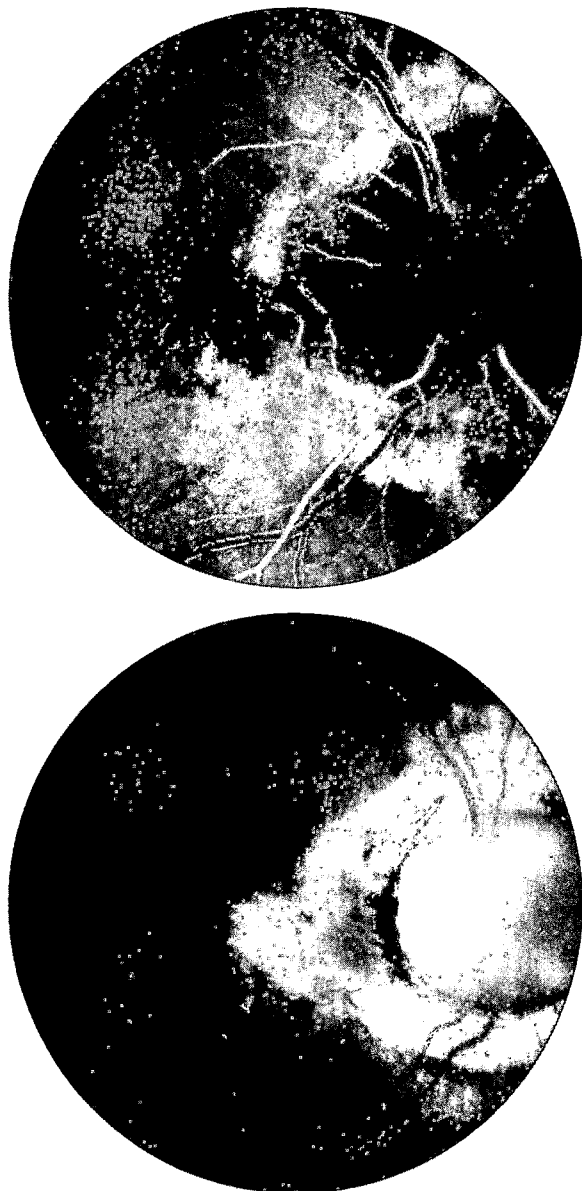
Figure (Sobol and associates). Top, Fluorescein angiogram (early phase) shows subretinal neovascular network adjacent to the disk, with blockage corresponding to the subretinal hemorrhage. Bottom, Diffuse leakage (late phase) from subretinal neovascular network.

extrafoveal location, clinicians should be aware of its potential occurrence in patients affected by the morning glory syndrome. The possible development of an extrafoveal subretinal neovascular membrane in this condition takes on added significance in those patients with good visual potential. Early detection of subretinal neovascular membrane can be enhanced by the use of Amsler grid testing. Patients with morning glory disk syndrome who are capable of noting early signs and symptoms of a subretinal neovascular process should be instructed in the use of Amsler grids and advised to monitor the affected eye on a routine basis.

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Delayed Increased Intraocular Pressure After Nd:YAG Laser Posterior Capsulotomy in a Patient Treated With Apraclonidine

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Marked increase of intraocular pressure is the most frequent complication following Nd:YAG laser posterior capsulotomy.[1] Apraclonidine, an alpha adrenergic agonist, has been reported to lower significantly the intraocular pressure increase when instilled one hour before and immediately after the procedure.[2,3] We treated a patient who developed a marked delayed increase of intraocular pressure after Nd:YAG laser posterior capsulotomy and lysis of pigment off the anterior surface of the intraocular lens, despite treatment with apraclonidine 1%.

A 73-year-old white man with advanced primary open-angle glaucoma and anatomically narrow angles had previously undergone argon laser peripheral iridectomy and laser trabeculo-

plasty in both eyes. Additionally, both eyes underwent extracapsular cataract extraction with intraocular lens implantation and filtering procedure that required later YAG capsulotomy in both eyes. The capsulotomy in the left eye was uneventful. In the right eye, however, there were also dispersed pigment deposits on the anterior surface of the intraocular lens that were thought to contribute to the patient's complaint of glare. A combined posterior capsulotomy and pigment lysis was therefore performed with the Q-switched, Nd:YAG laser (29.6 mJ aimed at the posterior capsule and 16 mJ directed at the pigmented deposits). One drop of apraclonidine 1% was instilled to the patient's eye before and at the end of the procedure. One hour later intraocular pressure was 20 mm Hg. The patient was instructed to administer prednisolone acetate 1% drops three times daily to the operated on eye in addition to his glaucoma medications. The following morning he complained of ocular pain and marked reduction of vision in the right eye. On examination visual acuity was 20/300 and intraocular pressure was 60 mm Hg. He was treated with systemic hyperosmotic agents plus topical timolol and additional apraclonidine. Intraocular pressure remained in the mid 30s for the next 24 hours and then decreased to the low teens with recovery of 20/40 visual acuity on the third day after the procedure. No progression of visual field loss occurred, and one year later visual acuity was 20/25 and intraocular pressure was 13 mm Hg.

The absence of an early postlaser pressure increase does not preclude a markedly increased intraocular pressure 24 to 48 hours later, even when apraclonidine is used at the time of the operation. We now recommend that patients with severe glaucomatous damage be seen not only early after these procedures, but also 24 hours later. Whether the high intraocular pressure measured after 24 hours represents a late pressure increase or a persistent rise that was attenuated by the apraclonidine cannot be determined. The marked increase in intraocular pressure observed in our patient may be related to the "extended procedure" that was actually a combination of posterior capsulotomy and pigment lysis from the anterior surface of the intraocular lens. Released pigment particles could have reached and obstructed the trabecular meshwork. Additionally, the shock waves created by aiming the beam at the pigment deposits on the anterior lens surface may also have caused damage to the trabeculum more than in a typical posterior capsulotomy, where the intraocular lens serves as a barrier.

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The Onset of Malignant Glaucoma After Prophylactic Laser Iridotomy

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A 43-year-old woman had bilateral glaucoma, since the age of 16 years, which progressed to absolute glaucoma in the right eye, and chronic closed-angle glaucoma in the left eye. Corrected visual acuity in the left eye was 20/30. The intraocular pressure was less than 20 mm Hg while using topical pilocarpine 4% every eight hours, timolol 0.5% every 12 hours, and acetazolamide (250 mg once daily). The central anterior chamber was deep and gonioscopy showed a slit-like open angle. The visual field was normal. Three months earlier the patient had undergone laser iridotomy in the left eye because of an intraocular pressure of 28 mm Hg and a closable angle. The intraocular pressure remained slightly increased (21 to 24 mm Hg) and the angle was closable, though the coloboma of the iris was patent.

She was admitted to the ophthalmology department because of a sudden onset of pain and

blurred vision in the left eye. Visual acuity was 20/100; the intraocular pressure was 38 mm Hg with mild conjunctival injection and a clear cornea. The anterior chamber was shallow; the pupil was 2 mm in diameter and not responsive to light. A patent iridotomy, incipient cataract, and normal fundus with cup/disk ratio of 0.6 were observed. Gonioscopy disclosed a completely closed angle.

The patient was treated initially with hyperosmotic agents and topical pilocarpine 4%. After three days of unsuccessful medical treatment trabeculectomy was performed.

Postoperatively the intraocular pressure rose to 45 mm Hg with a flat anterior chamber. Malignant glaucoma was diagnosed and intensive treatment with cycloplegics and mannitol was given. The anterior chamber did not reform and air was injected into the anterior chamber. This was followed two days later by pars plana vitrectomy with Healon injection to the anterior chamber. Despite transient improvement the pressure again rose with recurrent shallowing of the anterior chamber. Deep vitrectomy to aspirate the aqueous from the vitreous resulted in maintenance of normal intraocular pressure and a moderately deep anterior chamber. Two weeks later the intraocular pressure rose suddenly to 50 mm Hg, and a shallow anterior chamber was noted. Pars plana vitrectomy and lensectomy were successfully performed.

Five months postoperatively the best-corrected visual acuity was 20/40. Slit-lamp examination of the left eye showed a clear cornea, deep anterior chamber, and intraocular pressure of 15 mm Hg without medical treatment.

On reassessing the development of our patient's illness we think it is possible that the course of malignant glaucoma began after the prophylactic laser iridotomy that she had undergone three months previously. This could explain the lack of response to conventional treatment (pilocarpine and acetazolamide) that she received on admission. The administration of a cycloplegic at this stage might have prevented the progression of the malignant glaucoma and the ensuing surgical intervention.

Amantadine and Corneal Deposits

F. T. Fraunfelder, M.D.,
and S. Martha Meyer, B.S.

Inquiries to F. T. Fraunfelder, M.D., Department of Ophthalmology, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Rd., Portland, OR 97201-3098.

Amantadine hydrochloride (Symmetrel) is used in the management of Parkinson's disease, tardive dyskinesia, and the prophylaxis of influenza A_2 (Asian) virus infections. Ocular side effects are rare; however, blurred vision, sudden loss of vision, colored lilliputian visual hallucinations, oculogyric crises, and mydriasis have been reported.[1-3] These side effects appear to be dose-related and are reversible.[3]

The National Registry of Drug-Induced Ocular Side Effects has received nine case reports of corneal lesions associated with the use of oral amantadine hydrochloride. The corneal pattern seen in the affected patients was diffuse, white punctate subepithelial opacities, more prominent inferonasally, occasionally associated with a superficial punctate keratitis, corneal epithelial edema, and markedly reduced visual acuity. The dosage of amantadine was between 200 and 400 mg per day. The interval between therapy initiation and onset of the corneal reaction was one to two weeks. After discontinuation of drug use, the keratopathy disappeared in all patients usually in a few weeks; however, a six-week recovery period was necessary in one patient. Oral amantadine hydrochloride was reinstituted in two patients, and the corneal deposits recurred.

A cause-and-effect relationship is highly likely, since the corneal deposits resolved upon removal of the drug, and recurred in both patients in whom it was reinstituted. The superficial corneal deposits, associated edema and superficial punctate keratitis suggest the presence of the drug in the tear film. A 10-μl tear sample would contain 1.5 ng of amantadine hydrochloride, which is ten times lower than the assay limit of 20 ng (personal communication, E. I. DuPont DeNemours & Co., Newark, Delaware). Amantadine hydrochloride has, however, been found in other secreted fluids, such as saliva[4] and nasal mucus.[5] As with other oral agents, such as vitamin A,[6] which are secreted from various glands, including the lacrimal glands, amantadine hydrochloride may be secreted in the tear film thereby causing corneal deposits and corneal irritation.

There is a growing list of drugs[3] which are probably secreted by the lacrimal gland into the tear film. These drugs can cause corneal, conjunctival, or eyelid irritation, punctal occlusion, or corneal deposits based on the degree of toxicity of the offending drug. Amantadine hy-

drochloride in all probability can now be added to this list.

The National Registry of Drug-Induced Ocular Side Effects appreciates reports from clinicians of suspected drug-induced or chemical-induced ocular side effects. Without these, this report would not have occurred.

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Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Anatomy of Arteriovenous Crossings in Branch Retinal Vein Occlusion

EDITOR:

In the article, "Anatomy of arteriovenous crossings in branch retinal vein occlusion," by D. Weinberg, D. G. Dodwell, and S. A. Fern

(Am. J. Ophthalmol. 109:298, March 1990), the authors describe the occurrence of venous overcrossings at two of 82 vein occlusion sites. They did not consider that those two cases might not have been overcrossings.

I have observed the development of a bridge-type overcrossing collateral at a branch vein undercrossing obstruction site. The angiographic appearance was identical to that depicted in the article and termed, by the authors, as an overcrossing obstruction. I believe it remains to be proven that venous obstruction develops to any significant degree at an overcrossing.

W. REX HAWKINS, M.D.
Houston, Texas

Reply

EDITOR:

We appreciate Dr. Hawkins's interest in and comments on our article. Based on a previous observation, he proposes that the two cases that we reported as branch retinal vein occlusions at venous overcrossings could actually represent occlusions at arterial overcrossings, with secondary bridging venous collaterals. Although we cannot categorically dismiss this possibility, we are confident of our observations and have scientific evidence to support our conclusions.

Vein-to-vein collaterals form because of expansion of preexisting capillary channels.[1] In experimental branch retinal vein occlusions, these collaterals were seen to originate from capillaries deep in the retina.[2] This information is inconsistent with the development of a collateral vessel bridging over a large artery, which lies in the superficial layers of the retina. We would be most interested to see the case Dr. Hawkins described. If it evolved as he states, an alternate mechanism of collateral formation must be considered.

Clemmett[3] reported the appearance of a branch retinal vein occlusion at a venous overcrossing three weeks after the onset of symptoms. It would be unusual for such a well-developed collateral to form in such a short time.

If Dr. Hawkins's argument is correct, it does not contradict our basic assertion that branch vein occlusion at venous overcrossings are rare. The question is whether or not branch retinal vein occlusions ever occur at venous

overcrossings. We maintain that the evidence supports our assertion that they rarely do.

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————————— Reply —————————

EDITOR:

In our article, we were referring in general to the treatment of Lyme disease. In children under 9 years of age and pregnant women, treatment with tetracycline should be avoided. We thank Drs. Noel and Clarke for raising this issue.

KEITH B. SEIDENBERG, B.A.
MARTIN L. LEIB, M.D.
New York, New York

Orbital Myositis With Lyme Disease

EDITOR:

In the article, "Orbital myositis with Lyme disease," by K. B. Seidenberg and M. L. Leib (Am. J. Ophthalmol. 109:13, January 1990), the authors state that "Optimal treatment of Lyme disease in its different stages is being studied. Presently a course of oral tetracycline or doxycycline for ten days to three weeks is advised for early disease." In the 5-year-old child described in this report, tetracycline would not be the preferred course of treatment. For children less than 9 years of age, penicillin V, 15 mg/kg of body weight per day (not less than 1 g per day and not more than 2 g per day) in divided doses is recommended.[1] If the patient is allergic to penicillin, erythromycin 30 mg/kg of body weight per day in divided doses is recommended. Antimicrobial therapy is continued for ten to 20 days.

Tetracycline is to be avoided because of the deleterious effect to the secondary dentition in young children.[2]

LEON PAUL NOEL, M.D.
WILLIAM N. CLARKE, M.D.
Ottawa, Ontario, Canada

Tight Scleral Flap Trabeculectomy With Postoperative Laser Suture Lysis

EDITOR:

In the article, "Tight scleral flap trabeculectomy with postoperative laser suture lysis," by S. Melamed, I. Ashkenazi, J. Glovinsky, and M. Blumenthal (Am. J. Ophthalmol. 109:303, March 1990), the authors found that releasing trabeculectomy sutures postoperatively with the use of the argon laser is an effective means of reducing intraocular pressure and maximizing bleb survival. Lieberman[1] and Hoskins and Migliazzo[2] previously reported similar success. Using the widely available, four-mirror goniolens to compress the overlying conjunctiva and measures similar to those previously reported, I too have been impressed by the technique's ability and safety in enhancing bleb formation after a guarded glaucoma operation.

Based on seven years' experience with this technique, the only observation I can add is that suture lysis rarely is successful if performed later than ten days after trabeculectomy despite massage. The massage technique

I prefer is to moisten a cotton-tipped applicator and to apply it perpendicularly to the cornea, pressing centrally toward the optic nerve. This almost invariably results in an increased bleb after the suture lysis. If this is ineffective, applying the moistened tip at the edge of the lysed suture at the corneoscleral limbus can deform the sticking edges of the trabeculectomy flap, and allow for new egress of aqueous.

MARC F. LIEBERMAN, M.D.
San Francisco, California

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Reply

EDITOR:
    We appreciate Dr. Lieberman's comments and agree with his observations concerning the efficacy of laser suture lysis after filtration surgery. The beneficial effect on long-term intraocular pressure control by making the trabeculectomy a full-thickness sclerostomy has been reported.[1] We were glad to learn that transconjunctival suture lysis is also technically feasible by using a four-mirror goniolens. We believe that any transparent object able to compress the conjunctiva and make the sutures visible is appropriate for this treatment.

Additionally, we agree with Dr. Lieberman's comment regarding the poor rate of success if laser suture lysis is performed ten days or later postoperatively. In our experience, the procedure should be performed two to three days after surgery. This is the optimal time because the conjunctiva is already adherent to the corneoscleral limbus and there is no subconjunctival fibrosis, which enables good bleb formation. Because there is still a danger to developing wound leaks, however, we do not recommend digital massage at that early stage.

SHLOMO MELAMED, M.D.
ISAAC ASHKENAZI, M.D.
JOSEPH GLOVINSKI, M.D.
MICHAEL BLUMENTHAL, M.D.
Tel Hashomer, Israel

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BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Greer's Ocular Pathology, ed. 4. By David R. Lucas. Oxford, Blackwell Scientific Publications, 1989. 339 pages, index, illustrated. $99.95

Reviewed by ZEYNEL A. KARCIOGLU
New Orleans, Louisiana

The fourth edition of this text describes in a traditional manner the basic histopathologic features of frequently encountered ocular disorders. The 18 chapters are organized primarily by anatomic components of the eye and adnexae. Chapter 1, on inflammation and immunopathologic mechanisms, is useful for the beginner; it paves the way to more specific disease processes covered in later chapters. Ocular inflammations secondary to specific agents, such as fungal endophthalmitis, toxoplasmosis, cytomegalovirus retinitis, and the like, are detailed with photomicrographs. In Chapter 3, however, the syndromes that cause uveitis are covered superficially with only four figures, and there are no textual references from some of the sections, including ulcerative colitis, Fuchs' iridocyclitis, and psoriasis. "Idiopathic Intraocular Inflammation" seems a poor title for Chapter 3 because it includes specific entities such as Behçet's disease, ankylosing spondylitis, and Reiter's syndrome.

A more conventional division of anterior segment anatomy (cornea and sclera in one chapter, conjunctiva in the next) would be preferable to combining them in Chapter 5. Additionally, corneal pathology needs more emphasis; only 30 pages are allocated for Chapter 5. The coverage of corneal degenerations and dystrophies suffers greatly from the limited written and illustrative material. Despite space limitations, large electron micrographs have been used, instead of using inserts or side-by-side arrangement for key figures to reserve space for a more complete text.

The chapters concerning retina, tumors of neuroepithelium, and choroid are well organized and easy to read with pertinent, good quality photomicrographs. Chapters 4 and 18, related to trauma and sympathetic ophthalmia, are also well written, but should be combined. Areas related to orbit, eyelids, and lacrimal drainage apparatus are brief and sparsely illustrated. Although some orbital lesions are also mentioned elsewhere in the text, it is impossible to cover diseases of the orbit and lacrimal apparatus in 15 pages, particularly when inflammatory diseases, thyroid orbitopathy, and cystic lesions are also included.

Most of my criticisms are rather minor and do not seriously detract from the text's value. This textbook is well suited for medical students interested in basic ophthalmology, and for ophthalmologists in training and in practice who are interested in ophthalmic pathology. It is not structured for everyday differential diagnosis by the ophthalmic pathologist or general pathologist. Current specialized diagnostic pathology techniques including immunohistochemistry, fine needle aspiration biopsy, flow cytometry, cytomorphometry, and the like are not covered. Even with these limitations, however, the book is a concise reference.

Glare and Contrast Sensitivity for Clinicians. Edited by M. Princeton Nadler, David Miller, and Daniel J. Nadler. New York, Springer-Verlag, 1990. 150 pages, index, illustrated. $69

Reviewed by DOUGLAS D. KOCH
Houston, Texas

This is the first clinically oriented book on glare and contrast sensitivity testing to be published in 17 years. Appropriately enough, one of the authors (David Miller) was a coauthor of the earlier text (Miller, D., and Benedek, G.: Intraocular Light Scattering. Springfield, Illinois, Charles C Thomas, 1973). The authors' stated purpose is to "educate clinicians . . . in language they could understand." In this task, the text is largely successful.

The book begins with a section entitled "Terms and Concepts," which is an extremely useful glossary. This section alone will justify its purchase for some readers. The authors have tackled concepts as complex as "modulation transfer function" and "Fourier's theory" and

as mundane as "clear sky" and "black light." Most definitions are understandable, although some, such as units used in photometry, suffer from a lack of clarity.

The remainder of the book is loosely organized into three introductory chapters, four chapters on glare and contrast sensitivity loss in specific ocular diseases, and several chapters on standardization of these tests, principles, and photographic applications. This book suffers from the limitations of a multiauthored text. The rationale for the organization of the book is unclear, and there is considerable overlap among the chapters. For example, contrast sensitivity is defined and discussed in generic terms in at least ten of the 12 chapters.

Despite this lack of continuity, there are many highlights. Wolfe's chapter on contrast sensitivity testing is an elegant introduction to the principles and underlying physiology. Miller and Nadler's chapter on light scattering contains many wonderful everyday examples, ranging from snow goggles invented by Eskimos 2,000 years ago to glare systems designed to camouflage the Suez Canal.

For clinicians the strengths of this text lie in the early chapters that cover concepts and in the middle chapters that outline the uses of these tests in various ocular disorders. The chapter on contrast sensitivity and neuro-ophthalmic disease by Storch and Bodis-Wollner is a particularly complete review of what is known about contrast sensitivity loss in a variety of ophthalmic diseases.

Unfortunately, none of the chapters present a complete overview of currently available devices for measuring contrast sensitivity or glare. Certain devices, such as the Regan Low Contrast Acuity Charts and the True Visual Acuity device, are not mentioned in the text. Clinicians may also be frustrated by the relative lack of information on specific clinical applications of these tests. In this regard, the chapter "Diabetes Mellitus and Visual Function," by Cavallerano and Aiello, is an exception in that it provides three case histories describing particular applications and results of contrast sensitivity testing in patients with diabetic retinopathy.

In fairness to the authors, many of the deficiencies in this book reflect deficiencies in the field in general. There is inadequate standardization among tests, and the clinical implications of test scores are often poorly understood. In many respects, this field is in its infancy and the variety of opinions and approaches that are

covered in this text represent the scope of ongoing activities in this area.

This book provides an excellent starting point for anyone wishing to undertake an in-depth study of glare and contrast sensitivity testing. It will be useful to practicing physicians, residents, academicians, and other ophthalmic professionals seeking to learn more about these fundamental aspects of vision testing.

Ophthalmic Surgery. Principles and Practice, ed. 2. Edited by George L. Spaeth. Philadelphia, W. B. Saunders Company, 1990. 776 pages, index, illustrated. $125

Reviewed by ROBERT C. DREWS
St. Louis, Missouri

The value of a fine general textbook on ophthalmic surgery to residents and fellows is obvious. The chapters on surgical basics are as worthy for the excellent homespun philosophy and ethics that they contain as they are for the mechanics.

A practitioner who is actively engaged in general ophthalmic surgery uses a text such as this for a foundation and for an understanding of techniques that are not performed regularly. This volume is excellent in this respect. I particularly enjoyed the chapters on surgery of the orbit and plastic surgery. The chapter on glaucoma surgery could stand as a book in its own right with 142 pages and 150 references. Those looking for the latest nuances in surgical technique in rapidly evolving areas, however, should know better than to look in a textbook, since it takes about two years to get such a book published. For example, the chapter on ophthalmic lasers is subtitled "Current Status" but includes no references after 1985 and makes no mention of the excimer laser.

I was disappointed that the discussion of corneal graft failure did not include the Khodadoust line. I'm still not clear about the terms, "90 degrees away," "overlying," and "adjacent" to describe corneal topography, keratography, and corneal incisions. I grant that this is difficult information to convey, however, and the chapter on radial keratotomy is one of the best I have ever read. Likewise, I was disap-

pointed to find no mention of the use of lasers in the chapter on plastic surgery.

The typesetting and editing are excellent. The illustrations are superb. The book is worth having just for them. Hats off to a job well done and a worthy addition to our libraries.

enced the development of models of visual perception. The title, "Seeing Contour and Colour," epitomizes the idea that different aspects of a visual scene may be segregated but simultaneously analyzed. Most of the papers are concerned with the geniculostriate pathway.

Books Received

Medical Abbreviations. 7,000 Conveniences at the Expense of Communications and Safety, ed. 5. By Neil M. Davis. Huntingdon Valley, Pennsylvania, Neil M. Davis Associates, 1990. Softcover, 158 pages. $9.95

As the subtitle suggests, this book does not encourage the use of abbreviations. It underlines the potential for confusion and error by listing several different meanings for many of the abbreviations. For example, CF not only means "count fingers," but also may mean cystic fibrosis, complement fixation, cardiac failure, coronary flow, caucasian female, contractile force, Christmas factor, cisplatin and fluorouracil, and cancer-free. Apparently patients have been instructed to put the medicine in their left eye because the prescription said "per OS," and in the right eye because the prescription said "OD," meaning "once daily."

Ophthalmologists are among the worst offenders; our charts are notoriously incomprehensible. Residents should be taught to take the time to make their notes intelligible.

Seeing Contour and Colour. Edited by J. J. Kulikowski, C. M. Dickinson, and I. J. Murray. Oxford, Pergamon Press, 1989. 818 pages, index, illustrated. $270

This thick volume contains the proceedings of a conference held in Manchester, England, in 1987. The theme was the way in which the ideas associated with parallel processing have influ-

The Book List

Clinical Procedures for Ocular Examination. By Nancy B. Carlson, Daniel Kurtz, David A. Heath, and Catherine Hines. East Norwalk, Connecticut, Appleton & Lange, 1990. Softcover, 251 pages, index, illustrated. $35

Ophthalmology Oral History Series. A Link With Our Past. An Interview With Harold Glendon Scheie, M.D. By Sally Smith Hughes. San Francisco, The Foundation of the American Academy of Ophthalmology, 1989. Softcover, 355 pages, index, illustrated. $55

Ophthalmology Oral History Series. A Link With Our Past. An Interview With Thomas David Duane, M.D. By Sally Smith Hughes. San Francisco, The Foundation of the American Academy of Ophthalmology, 1989. Softcover, 178 pages, index, illustrated. $55

Sodium Hyaluronate in Anterior and Posterior Segment Surgery. Edited by Ronald G. Michels, Walter J. Stark, and Mario Stirpe. Padova, Italy, Liviana Press, 1989. 131 pages, illustrated. $35

A Synopsis of Ophthalmology, ed. 5. By J. L. C. Martin-Doyle and Martin H. Kemp. Bristol, England, John Wright & Sons Ltd., 1975. Softcover, 284 pages, index. $24.95

Obituary

DAVID SHOCH
1918-1990

David Shoch, president of the Ophthalmic Publishing Company, abstract editor of THE JOURNAL since 1964, and long-time secretary of the Heed Ophthalmic Foundation, died May 8, 1990, after a short illness.

His death caused me to recall many experiences over nearly a half a century of friendship. When we first met in 1945 he was an intern at Cook County Hospital with no particular interest in ophthalmology. The medical faculty at Northwestern University had high hopes for him to bridge biochemistry and clinical medicine. There were great plans for a career in gastroenterology, pediatrics, or biochemistry. After he was stationed at the School of Aviation Medicine at Randolph Field and discovered ophthalmology through the brilliant group gathered there by Victor Byrnes, David returned to Northwestern and a research fellowship in ophthalmology. This was followed by a residency at Cook County, and a partnership with Derrick Vail.

For many years we lunched together monthly. Shortly before he last entered the hospital David reminisced for the first time. Perhaps he anticipated I would be writing this for THE JOURNAL. He quoted his father that one should have a talent for luck. He credited his high school Latin teacher with stimulating his life-long interest in languages. His chemistry professor at City College recommended him to both the University of Maryland and Northwestern University; Northwestern replied first. After stumbling in an assignment in pediatrics, David concentrated on its study and the pediatrics professor subsequently introduced him to Trudy whom he later married.

David emphasized the difference between his background and that of Dr. Vail but he followed Derrick in many positions: president of the Ophthalmic Publishing Company, president of the Academy, and the American Ophthalmological Society, and chairman of the Department of Ophthalmology at Northwestern.

David forever changed the style of the Chicago Ophthalmological Society annual clinical conference when he invited an enormous group

David Shoch
1918-1990

to his home for an al fresco dinner under a brightly striped marquee. Thereafter the Society celebrated its clinical conference with a banquet although never again at the president's home.

From this dinner at the Shochs emerged a little group, the Ophthalmological Chowder, Marching, and Singing Society, that for the next 25 years annually journeyed to Stratford, Ontario, to Aspen or to festivals for plays, concerts, and musicals.

For many years David and I traveled together to meetings of the Academy and its various committees, to the Association of University Professors in Ophthalmology meetings, and to international congresses. There were hilarious events: getting lost in the Loire valley and orienting ourselves only by sighting a fabulous chateau in the distance; locking theater tickets and car keys in the trunk of a rented car; an elaborate dinner in the upper-deck sky lounge of a 747 airliner en route to Japan.

In many respects the division of the Academy into ophthalmology and otolaryngology is

mainly due to David. Two ophthalmologists on the Council strongly opposed reorganization. Other ophthalmic members often failed to attend meetings, and David and I were often the only two present who believed that both ophthalmology and otolaryngology would benefit from independent groups. Since I presided and could not participate in debates, David was often the only voice supporting a reorganization. In 1975 the Academy election gave the groups that opposed reorganization only 13% of the vote and it was evident that both the ophthalmologists and the otolaryngologists recognized the need for two groups. Well do I remember David returning from the count of the secret ballots, long after adjournment of the general meeting, to announce the final vote tally.

David followed Herbert Haessler as abstract editor in 1964. Edward Jackson had founded the Ophthalmic Year Book in 1908 and the abstract section was its successor in the new series of THE JOURNAL. In 1964 when David took over, some 150 abstracts were published each month. A large group of collaborators prepared the abstracts and here David's skill with languages was important for he was able to wrestle into passable English the some 1,800 abstracts submitted annually. Since 1964 David never missed a deadline; the July 1990 Abstract Section is the first not edited by him. The advent of the many other abstracting services and the gradual change in ophthalmic practice in which the competent ophthalmologist is not expected to be familiar with the world literature led to the gradual shrinkage in abstract coverage.

The Heed Ophthalmic Foundation has had important Chicago roots since Derrick Vail persuaded Thomas Heed in 1946 to establish the Foundation. David became secretary-treasurer of the Foundation in 1967 and in 1983 became executive secretary. From a modest beginning the Foundation has emerged as an important group awarding some 20 fellowships annually to some 100 applicants selected by the directors.

Dr. Shoch was born June 10, 1918, in Warsaw, Poland. His parents, his sister, and he came to the United States in 1920. He attended the public schools in New York City, and received a bachelor of science degree from the College of the City of New York in 1938. In 1939, he received a master of science degree from Northwestern University and in 1943 a doctor of philosophy degree in biochemistry. His doctor-

al thesis received the Sigma Xi thesis prize. In 1945, he received the doctor of medicine degree from Northwestern. He entered the United States Army Medical Corps immediately after his internship at Cook County Hospital and was assigned to the School of Aviation Medicine at Randolph Field, Texas. He returned to Northwestern for a research fellowship in ophthalmology and then a residency at Cook County Hospital.

In 1953, he joined Derrick Vail in partnership. Vail was then editor of THE JOURNAL and chairman of the Department of Ophthalmology at Northwestern University. Dr. Vail had stopped operating that year and Dr. Shoch plunged into a major surgical and consultative practice. He succeeded Dr. Vail as professor and chairman of the Department of Ophthalmology in 1966 and served until 1983. He continued as professor at Northwestern until his death. He was chairman of the Department of Ophthalmology at Northwestern Memorial Hospital, the Veterans Administration Lakeside Hospital, and a consultant at Children's Memorial Hospital. He was president of the medical council of Northwestern Memorial Hospital and a member of the executive committee of the board of trustees of the Hospital. He edited the alumni bulletin of Northwestern University Medical School for ten years.

Dr. Shoch gave broadly of his talents to organized medicine. He was secretary for instruction and served on the committee for reorganization of the American Academy of Ophthalmology and Otolaryngology and, subsequently, on the committee on recertification. In 1963 he was president of the Chicago Ophthalmological Society and was president of the American Academy of Ophthalmology in 1981, when it became an entirely independent organization. In 1989, he was president of the American Ophthalmological Society when the Society celebrated the 125th year of its founding.

He was certified by the American Board of Ophthalmology in 1953 and was chairman of the Board in 1979. He served on the advisory council for ophthalmology of the American College of Surgeons and was chairman of the Association of University Professors of Ophthalmology (1972-1973). He represented the Academy on the Council of American Board of Medical Specialty Societies and was a delegate from the United States to the French Ophthalmological Society. He served as vice president

of the National Society for the Prevention of Blindness and was a director of the Illinois Society for the Prevention of Blindness.

Before entering ophthalmology, Dr. Shoch published widely about the gastrointestinal system. He was an expert on the enzymology of the lens and radiation cataract.

The committee on prizes of the American Ophthalmological Society voted earlier in this year to award Dr. Shoch the Society's highest honor, the Lucien Howe Medal. The chairman of the Award Committee of the Society, Robert Burns, noted that death had not diminished Shoch's contribution to ophthalmology, and the Committee and Society approved posthumous award of the medal May 21, 1990.

In April 1990 Shoch received the Alumni Medal of Northwestern University as its most distinguished graduate. This is the highest honor Northwestern awards to a graduate. He had received the Merit Award from the alumni association 15 years earlier. He was an inspirational teacher and his residents donated an oil portrait of him that now hangs in the Northwestern University Medical Library.

Dr. Shoch was an eternal student. He maintained his skills in Latin and was taking piano lessons at the Northwestern School of Music. In January of this year he traveled to Spain for lessons in conversational Spanish. He was a governor of the Chicago Orchestral Association and a devotee of modern poetry and art.

Dr. Shoch's wide interests made him a brilliant conversationalist. THE JOURNAL staff recall his discussions of art, music, literature (particularly French), and even Druids. His patients treasured him because he had that rare combination of diagnostic, technical skill and the ability to inspire hope and confidence on even the briefest of meetings.

He is survived by his wife Gertrude (Trudy) and two sons, John and James. The David Shoch professorial chair is being established by friends and alumni of the Department of Ophthalmology at Northwestern University Medical School.

FRANK W. NEWELL

ABSTRACT DEPARTMENT

British Journal of Ophthalmology

Retinal laser lenses: magnification, spot size, and field of view. Mainster, M. A., Crossman, J. L., Erickson, P. J., and Heacock, G. L. (Dept. Ophthalmol., Kansas Univ. Med. Ctr., 39th & Rainbow Blvd., Kansas City, KS 66103). Br. J. Ophthalmol. 74:177, 1990.

Proper use of ophthalmoscopic contact lenses for retinal photocoagulation requires knowledge of their comparative magnification, spot size, and field of view. We determined these parameters for four commonly used lenses, using data measured from optical components of the lenses and a commonly used photocoagulator slit-lamp and spot size changer. A Krieger lens has 8% more working field of view and 29% less magnification than a Goldmann lens. A Panfundoscope lens has 84% more working field of view and 24% less magnification than a Goldmann lens. A Mainster lens has 58% more working field of view and 3% more magnification than a Goldmann lens. For Goldmann, Krieger, Panfundoscope, and Mainster lenses, respectively, retinal spot size is 8%, 53%, 41%, and 5% greater than photocoagulator spot size settings. The field of view of each lens is increased in myopic and decreased in hyperopic patients. Anterior segment irradiance is higher than retinal irradiance for 1000 μm spot size settings with a Panfundoscope or Mainster lens, and this setting should be avoided, especially in patients with hazy ocular media. (4 figures, 4 tables, 14 references)—Authors' abstract

Biostatistical evidence for two distinct chronic open angle glaucoma populations. Schulzer, M., Drance, S. M., Carter, C. J., Brooks, D. E., Douglas, G. R., and Lau, W. (Dept. Med., Faculty of Med., Univ. British Columbia, 910 W. 10th Ave., Vancouver, BC, Canada V5Z 4E3). Br. J. Ophthalmol. 74:196, 1990.

Twenty-six eyes of 26 patients with low-tension glaucoma and 34 eyes of 34 patients with high-tension glaucoma were studied. Fifty-one measurements were available on each patient, including visual field indices, finger blood flow measurements, as well as hematological, coagulation, and biochemical and rheological variables. Multivariate analysis revealed two statistically distinct groups of patients, with low and high tension glaucoma cases equally distributed in both. The smaller group (15 patients) showed a suggestion of vasospastic finger blood flow measurements, and had a high positive correlation between the mean deviation index of field severity and the higher intraocular pressure (r = 0.715, p = 0.0008). The second, larger group (45 patients) showed disturbed coagulation and biochemical measurements, suggestive of vascular disease, and had no correlation between the mean deviation index and the highest intraocular pressure. (3 figures, 2 tables, 14 references)—Authors' abstract

Diabetes

Is insulinlike growth factor I associated with diabetic retinopathy? Dills, D. G., Moss, S. E., Klein, R., Klein, B., and Davis, M. (Univ. Wisconsin Med. School, Dept. Med., 600 Highland Ave., Madison, WI 53792). Diabetes 39:191, 1990.

Insulinlike growth factor I is the mediator of the growth-promoting effects of growth hormone and has been suspected of playing a role in the pathogenesis of proliferative diabetic retinopathy. However, previous attempts to correlate insulinlike growth factor I levels with proliferative diabetic retinopathy have yielded conflicting results. The authors determined insulinlike growth factor I levels in a large population-based study of 682 early-onset (diagnosed before 30 yr of age) adult (≥ 18 yr old) insulin-taking diabetic subjects. Proliferative diabetic retinopathy was found in 25% of the population. Insulinlike growth factor-I levels were measured by radioimmunoassay. The mean serum level of insulinlike growth factor I was 277 ± 108 μg/L (mean ± SD). Spearman

rank correlations showed statistically significant negative correlations between insulinlike growth factor I levels and age ($r = -0.51$, $P < 0.0001$), duration of disease ($r = -0.36$, $P < 0.0001$), and glycosylated hemoglobin ($r = -0.09$, $P < 0.05$). There was a significant trend ($P < 0.001$) toward decreasing risk of proliferative diabetic retinopathy with increasing insulinlike growth factor I. However, after controlling for duration of diabetes, glycosylated hemoglobin, diastolic blood pressure, and the presence of proteinuria and/or creatinine $\geq$ 265 μM in a multiple logistic regression model, insulinlike growth factor I was not significantly associated with proliferative diabetic retinopathy. These data suggest that insulinlike growth factor I may not be a risk factor for the development of proliferative diabetic retinopathy. (3 figures, 5 tables, 34 references)—Authors' abstract

Experimental Eye Research

Light transmission of the cornea in whole human eyes. Beems, V. M., and Van Best, J. A. (Dept. Ophthalmol., Leiden Univ. Hosp., P.O. Box 9600, 2300 RC Leiden, the Netherlands). Exp. Eye Res. 50:393, 1990.

The transmission of the cornea for light in the wavelength range 450-1000 nm was measured in steps of 50 nm by means of a photodiode implanted into the anterior chamber of whole human donor eyes. In the range from 450 nm up to 600 nm the percentage transmission was found to increase with wavelength from 80% up to 94%. In the range from 600 nm up to 1000 nm the percentage transmission was between 95% and 98%. The corneal transmission for donors younger than 45 yr (n = 3, 22-43 yr) did not differ significantly from that of donors older than 45 yr (n = 5, 67-87 yr) at any wavelength. (2 figures, 2 tables, 5 references)—Authors' abstract

Journal of Neurology, Neurosurgery and Psychiatry

Regional cerebral blood flow (rCBF) and cerebral vasoreactivity in patients with retinal is-

chaemic symptoms. Kerty, E., Russell, D., Bakke, S. J., Nyberg-Hansen, R., and Rootwelt, J. (Dept. Neurol., Rikshopitalet, The National Hospital, 0027, Oslo 1, Norway). J. Neurol. Neurosurg. Psychiatry 52:1345, 1989.

Regional cerebral blood flow and cerebral vasoreactivity were assessed in 28 consecutive patients who presented with retinal ischemic symptoms, without clinical or cerebral CT evidence of cerebral ischemia. Regional cerebral blood flow was measured using xenon-133 inhalation and single photon emission computed tomography before and 20 minutes after the intravenous administration of 1 g acetazolamide. The findings suggest that patients with retinal ischemic symptoms alone due to carotid atherosclerosis often have a carotid lesion which is of hemodynamic significance with regard to cerebral perfusion and vasoreactivity. Furthermore, localized areas with reduced cerebral perfusion may also be present in some patients, without evidence of precerebral carotid occlusive disease. (2 figures, 3 tables, 28 references)—Authors' abstract

Ocular inflammatory changes in established multiple sclerosis. Graham, E. M., Francis, D. A., Sanders, M. D., and Rudge, P. (Natl. Hosp. Nervous Dis., Maida Vale, London W9 1TL, United Kingdom). J. Neurol. Neurosurg. Psychiatry 52:1360, 1989.

Fifty consecutive patients with clinically definite multiple sclerosis were studied to assess the prevalence of concomitant uveitis. Asymptomatic ocular inflammatory changes were found in nine patients (18%) and appeared to show a positive correlation with severe and progressive disease. Conversely uveitis was uncommon in the presence of established optic atrophy which suggests a negative influence on its pathogenesis. In the absence of optic atrophy inflammatory changes in the eye may be a valuable index of disease activity. (1 figure, 2 tables, 13 references)—Authors' abstract

Disturbances in ocular sympathetic function and facial blood flow in unilateral migraine headache. Drummond, P. D. (Psychol. Sec.

Murdoch Univ., Murdoch, 6150, Western Australia). J. Neurol. Neurosurg. Psychiatry 53:121, 1990.

The relationship between thermographic asymmetry in various parts of the face and indices of ocular sympathetic outflow was examined in 80 patients with unilateral migraious headache. Both during and between episodes of headache, the pupil on the symptomatic side dilated more slowly and less extensively in darkness than the opposite pupil, indicating that ocular sympathetic outflow was compromised in some patients. In such cases the upper forehead and orbital region were warmer on the symptomatic side during migraine. In contrast to these signs of a reduction in cervical sympathetic outflow, eyelid separation was greater on the symptomatic side in patients with headache on the side that was usually affected. During the headache-free interval no consistent thermographic asymmetry was detected and eyelid separation was similar on both sides. These findings suggest that extracranial vascular changes and ocular sympathetic dysfunction during migraine are secondary to activation of trigeminal-vascular reflexes or to antidromic release of vasoactive substances from trigeminal nerve terminals. A secondary deficit in the sympathetic pathway to the symptomatic pupil could also prevent the expression of an increase in sympathetic outflow during headache. (5 tables, 25 references)—Author's abstract

oblique underaction were retrospectively studied pre- and postoperatively. The data show that weakening the inferior oblique corrected the underaction of the superior oblique, and that overcorrection of the underacting superior oblique was unusual. Eyes were selected for study if superior oblique underaction coexisted with inferior oblique overaction preoperatively. The operation chosen for the inferior oblique in every case was determined by the quantity of inferior oblique overaction and whether prior surgery on the inferior oblique had been performed. A denervation and extirpation was the final inferior oblique weakening procedure in all except three of these eyes. Congenital or acquired superior oblique palsy cases were not included in this study. To eliminate eyes with superior oblique palsy, we excluded any patient with a history of serious head trauma; a vertical deviation in the primary position greater than 5 prism diopters except if caused by dissociated vertical deviation; the complaint of torsional diplopia controlled by an anomalous head posture; or a positive Bielschowsky head tilt test. The mean preoperative superior oblique action was −2.4 on a scale of 0 to 4, and this corrected to a mean postoperative action of −0.2, (p < .001). This was accompanied by a change in the mean inferior oblique action of +3.8 to −0.2, (p < .001). These same results were found regardless of the preoperative action of either the inferior or superior oblique. With regard to the postoperative superior oblique action, 22 cases were undercorrected, 2 were overcorrected and 102 were normal. (11 tables, 8 references)—Authors' abstract

Journal of Pediatric Ophthalmology and Strabismus

Response of coexisting underacting superior oblique and overacting inferior oblique muscles to inferior oblique weakening. Hunter, L. R., and Parks, M. M. (Med. Editing HSHH-CI-ME, Dept. Clin. Invest., Letterman Army Med. Ctr., Presidio of San Francisco, CA 94129-6700). J. Pediatr. Ophthalmol. Strabismus 27:74, 1990.

One hundred twenty-six eyes with inferior oblique overaction and coexisting superior

Morbidity and Mortality Weekly Report

Microsporidian keratoconjunctivitis in patients with AIDS. Orenstein, J. M., Seedor, J., Friedberg, D. N, Stenson, S. M., Tierno, P. M., Charles, N. C., Meisler, D. M., Lowder, C. Y., McMahon, J. T., Longworth, D. L., Rutherford, I., Yee, R. W., Martinez, A., Tio, F., and Held, K. (George Washington Univ. Med. Ctr., District of Columbia). Morbid. Mortal. Weekly Rep. 39:188, 1990.

From November 1989 through January 1990, five cases of ocular infections with microsporidia in patients with acquired inmunodeficiency syndrome (AIDS) were reported. Three cases were identified in New York City, one in San Antonio, and one in Cleveland. All five patients were homosexual men aged 29-46 years. The most common presenting manifestations were conjunctivitis or scleritis (all patients), foreign body sensation (four patients), blurred vision (three patients), and photophobia (three patients). Ophthalmologic examinations revealed conjunctival inflammation (all patients), decreased visual acuity (four patients), and diffuse punctate keratopathy (four patients). One patient had corneal inflammation, and one patient had corneal ulceration. Findings were bilateral in all patients. Concomitant, unilateral cytomegalovirus retinitis was noted in two patients. After routine bacterial and fungal cultures failed to identify plausible etiologic agents, corneal or conjunctival scrapings and/or biopsy specimens were obtained from all patients. Sections from these specimens prepared with Giemsa and other routine histologic stains contained numerous oval, dark-staining organisms consistent in morphology with microsporidian spores. Visualization of characteristic ultrastructure with transmission electron microscopy confirmed the diagnosis in all cases.

Two of the five patients died of other AIDS-related complications. No improvement in their ocular infections was noted before death despite attempted treatment with various topical antimicrobial (tobramycin, chloramphenicol, and sulfisoxazole), lubricating, and anti-inflammatory agents. Two other patients did not respond to therapy with topical antimicrobial agents (neomycin, propamidine isethionate, amphotericin, sulfacetamide, and trimethoprim/sulfamethoxazole); however, several weeks after therapy was discontinued the symptoms resolved. The reason for these improvements is unknown, but both patients coincidentally began systemic therapy with fluconozole or itraconazole for concomitant cryptococcal meningitis. Infection in the fifth patient failed to respond to topical preparations (cefazolin, propamidine isethionate, and clotrimazole); one cornea perforated, and the patient underwent emergency corneal grafting. The exact source of infection in all five cases remains unknown. (7 references)—Authors' abstract

Neurology

Complex visual disturbances in Alzheimer's disease. Mendez, M. F., Mendez, M. A., Martin, R., Smyth, K. A., and Whitehouse, P. J. (Dept. Neurol., St. Paul-Ramsey Med. Ctr., Jackson at University, St. Paul, MN 55101-2595). Neurology 40:439, 1990.

Although Alzheimer's disease involves visual association cortex, previous studies have not systematically investigated complex visual disturbances in Alzheimer's disease. We examined 30 community-based Alzheimer's diseased patients, 13 (43%) of whom had complex visual complaints, and compared them with 30 controls on 7 types of complex visual tasks. Despite preserved visual acuity and color recognition, the Alzheimer's diseased patients were impaired in the visual evaluation of common objects, famous faces, spatial locations, and complex figures. In the Alzheimer's diseased patients, we found that all 30 had disturbances in figure-ground analysis; 17 (57%) had difficulties visually recognizing actual objects ("agnosia"); those with worse dementia disability had the most complex visual disturbances; and a subgroup (6) with Balint's syndrome performed the most poorly on the complex visual tasks. This study demonstrates that a range of complex visual disturbances are common in Alzheimer's disease and suggests that they may result from the known neuropathology in the visual association cortex. (3 figures, 1 table, 39 references)—Authors' abstract

Stroke

Transient monocular visual loss patterns and associated vascular abnormalities. Bruno, A., Corbett, J. J., Biller, J., Adams, H. P., and Qualls, C. (Neurol. Ser. 127, V.A. Med. Ctr., 2100 Ridgecrest Dr. S.E., Albuquerque, NM 87109). Stroke 21:34, 1990.

To determine if certain transient monocular visual loss patterns predict the associated vascular abnormalities, the authors prospectively evaluated 100 consecutive patients. Each patient had hematologic tests, a carotid artery study (arteriography in 74, duplex ultrasono-

graphy in the remaining 26), and an ophthalmologic examination. Patients with altitudinal or lateralized transient monocular visual loss were more likely to have carotid artery stenosis, carotid artery ulceration, cardiac sources of emboli, or visible retinal emboli than patients with other visual loss patterns. The authors' findings suggest that altitudinal or lateralized transient monocular visual loss is primarily caused by embolism but that other visual loss patterns are usually caused by nonembolic mechanisms. (1 figure, 2 tables, 49 references)—Authors' abstract

NEWS ITEMS

International Congress on Myopia

The International Congress on Myopia will be held in Buenos Aires, Argentina, Sept. 17–20, 1990, at the Buenos Aires Plaza Hotel. For further information, write Secretariat of the Congress, Av. Pte. Sáenz Pēna 720 5°A, (1035) Buenos Aires, Argentina; Fax (541) 322-1328.

American College of Veterinary Ophthalmologists: Annual Meeting

The American College of Veterinary Ophthalmologists: Annual Meeting will be held Oct. 10–14, 1990, in Scottsdale, Arizona. For further information, write Dr. C. Sue West, Veterinary Ophthalmology Clinic, 4050 Broadview Rd., Richfield, OH 44286; telephone (619) 755-5136.

American Society of Cataract and Refractive Surgery: Symposium on Cataract, IOL and Refractive Surgery

The American Society of Cataract and Refractive Surgery: Symposium on Cataract, IOL and Refractive Surgery will be held April 7–10, 1991, in Boston, Massachusetts. For further information, write Lucy Santiago, Executive Administrator, American Society of Cataract and Refractive Surgery, 3702 Pender Dr., Suite 250, Fairfax, VA 22030; telephone (703) 591-2220.

Alabama Academy of Ophthalmology: Annual Meeting

The Alabama Academy of Ophthalmology: Annual Meeting will be held Aug. 1–5, 1990, in Panama City, Florida. For further information, write Alabama Academy of Ophthalmology, Annual Meeting Information, P.O. Box 11252, Birmingham, AL 35202-1252; telephone (205) 322-3084.

University of Miami—Bascom Palmer Eye Institute: Neuro-Ophthalmology Course

The University of Miami—Bascom Palmer Eye Institute: Neuro-Ophthalmology Course will be held December 6–8, 1990, in Miami, Florida. For further information, write University of Miami School of Medicine, Bascom Palmer Eye Institute, P.O. Box 015869, Miami, FL 33101; telephone (305) 326-6099.

University of Southern California School of Medicine: Ophthalmology—A Review for the Practicing Ophthalmologist

The University of Southern California School of Medicine Postgraduate Division with the Department of Ophthalmology will sponsor a course, Ophthalmology—A Review for the Practicing Ophthalmologist, Aug. 4–11, 1990, in Kamuela, Hawaii. For further information, write B. Johnson, USC School of Medicine, 1975 Zonal Ave., Los Angeles, CA 90033; telephone (213) 224-7051 or Fax (213) 225-4557.

Florida Society of Ophthalmology: 1990–1991 Officers

The Florida Society of Ophthalmology elected the following officers for 1990–1991: president, Emanuel Newmark, Atlantis; president-elect, Waite S. Kirkconnell, Tampa; first vice president, John R. Brayton, Jr., Pensacola; and second vice president, Louis R. Kurland, Hollywood.

Chicago Ophthalmological Society: 1990–1991 Officers and Council

The Chicago Ophthalmological Society elected the following officers and council for 1990: Lee Jampol, president; Elise Torczynski, vice-president; Karl W. Scheribel, president-elect; Thomas Deutsch, secretary/treasurer; and Paul Morimoto, corresponding secretary.

_____ Personals _____

Travis A. Meredith

Travis A. Meredith, professor of ophthalmology at Emory University has been named the

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director of the Vitreo-retinal Surgical Service at the Wilmer Eye Institute at Johns Hopkins Medical Institutions. A 1969 graduate of the Johns Hopkins School of Medicine and former Wilmer resident, Meredith has been a professor of ophthalmology at Emory University School of Medicine since 1984.

Hugh R. Taylor

Hugh R. Taylor of the Wilmer Institute, Johns Hopkins University, has been named the Ring-

land Anderson Professor of Ophthalmology at the University of Melbourne and Director of Eye Services at the Royal Victorian Eye and Ear Hospital, Melbourne, Australia. The professorship honors Dr. J. Ringland Anderson, who was a leading Australian ophthalmologist and Dr. Taylor's grandfather. Dr. Taylor trained in Melbourne before starting a fellowship at Wilmer in 1977. He joined the Wilmer faculty full-time in 1979 and has been the Associate Director of the Dana Center for Preventive Ophthalmology since that time.

AMERICAN JOURNAL

OF

OPHTHALMOLOGY

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*Glasser DB, Katz HR, Boyd JE, et al. Protective effects of viscous solutions in phacoemulsification and traumatic lens implantation. *Arch Ophthalmol.* 1989; 107:1047-1051.

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Pneumocystis carinii Choroiditis After Long-term Aerosolized Pentamidine Therapy

Pravin U. Dugel, M.D., Narsing A. Rao, M.D., David J. Forster, M.D.,
Lawrence P. Chong, M.D., George T. Frangieh, M.D., and Fred Sattler, M.D.

Pneumocystis carinii pneumonia is a major cause of morbidity and mortality in patients with the acquired immunodeficiency syndrome. When *P. carinii* is disseminated, the choroid may be involved and the infection is often fatal. We examined, treated, and followed up two patients who developed choroidal lesions typical of *P. carinii* while taking aerosolized pentamidine for prophylaxis. The choroidal lesions gradually resolved after three weeks of therapy with intravenous trimethoprim and sulfamethoxazole in one patient, and after three weeks of therapy with parenteral pentamidine in the other patient. The patients did not have clinical or laboratory evidence of *P. carinii* infection other than in the eye. It thus appears that early ophthalmologic examination may detect disease before it is threatening to sight and allow systemic therapy to be instituted before widely disseminated infection results in a fatal outcome.

MORE THAN 80% OF PATIENTS with the acquired immunodeficiency syndrome develop *Pneumocystis carinii* pneumonia, and in 60% of patients it is the initial opportunistic infection.[1]

Since 1981, more than 20,000 cases of *P. carinii* pneumonia have been reported to the Centers for Disease Control, and it is anticipated that by 1991, 75,000 to 100,000 cases will have been diagnosed.[2] Although initial treatment is generally effective, more than 60% of patients have a recurrence within one year, unless they receive appropriate prophylaxis.[3]

Aerosolized pentamidine is one such prophylactic therapy, and it prevents recurrence in approximately 80% of patients for up to one year.[4] Drug deposition, however, is limited primarily to the lung, and there have been increasing numbers of reports of extrapulmonary *P. carinii* infection. Presumably, extrapulmonary dissemination occurs during a previous episode of *P. carinii* pneumonia and reactivation occurs at these sites during prophylaxis with aerosolized pentamidine. The eye may be one such site of reactivation.

We treated two patients who had *Pneumocystis* choroiditis without extraocular signs, symptoms, or laboratory evidence of disseminated infection. These patients had *P. carinii* pneumonia confirmed by bronchoscopy five months and nine months earlier, respectively, and had taken monthly aerosolized pentamidine to prevent recurrence. Choroiditis resolved after three weeks of treatment with intravenous trimethoprim and sulfamethoxazole therapy in one patient and intravenous pentamidine therapy in the other patient.

Case Reports

Case 1

A 29-year-old man had intermittent blurred vision in both eyes for three weeks. He denied fever, cough, dyspnea, or other organ-specific symptoms. Five months earlier *P. carinii* pneu-

monia was diagnosed, for which the patient was hospitalized for two weeks and treated with 600 mg of aerosolized pentamidine once a day by means of a jet nebulizer. He improved rapidly on this regimen and was discharged without any symptoms. He was subsequently treated monthly with 150 mg of aerosolized pentamidine and remained completely asymptomatic.

On examination, his uncorrected visual acuity was 20/20 in each eye. The results of an external examination showed iridodialysis of the inferonasal iris of the right eye, consistent with a fishhook injury the patient received as a child. The anterior segment showed no signs of inflammation. Both eyes had 15 to 20 creamy-white, round or oval, slightly elevated choroidal lesions, most of which were in the posterior pole (Fig. 1, left). These lesions were ⅓ to ½ disk diameter in size. The retinal vessels showed no signs of vasculitis, and the overlying vitreous contained no inflammatory cells. There was a large scar approximately 3 disk diameters in the inferonasal fundus of the right eye, consistent with the previous injury. Fluorescein angiography showed early blockage with late staining (Fig. 2). No vasculitis or other sign of posterior segment inflammation was seen. The patient's vital signs were normal. Auscultation of the lungs was normal, and lymph nodes, liver, and spleen were not enlarged.

Based upon ophthalmoscopic examination, a diagnosis of extrapulmonary P. carinii infection was made. The patient was hospitalized for a three-week course of intravenous trimethoprim (20 mg/kg of body weight per day) and sulfamethoxazole (100 mg/kg of body weight per day). An extensive examination, which included chest radiographs, an arterial blood gas determination, liver function tests, and abdominal computed tomography, disclosed no abnormalities. His hospital course was uneventful except for mild fever and generalized rash that were treated with acetaminophen and antihistamines. Fundus photography and fluorescein angiography were performed weekly and showed a gradual decrease in the size of the choroidal lesions (Fig. 1, right).

Case 2

A 33-year-old man had blurred vision in both eyes, in the right eye worse than in the left, for one month. He had no other symptoms. His medical history was remarkable for an episode of P. carinii pneumonia nine months earlier that was treated with intravenous pentamidine (4 mg/kg of body weight per day) for two weeks, followed by two weeks of daily aerosolized pentamidine (150 mg by means of a jet nebulizer). Thereafter, he received monthly aerosolized pentamidine, 150 mg, by means of the jet nebulizer.

Visual acuity was R.E.: 20/60 and L.E.: 20/40. There were a few inflammatory cells in the anterior vitreous of each eye, and the optic nerves were hyperemic and swollen. The periphery contained lesions typical of cytomegalovirus retinitis, with confluent areas of hemor-
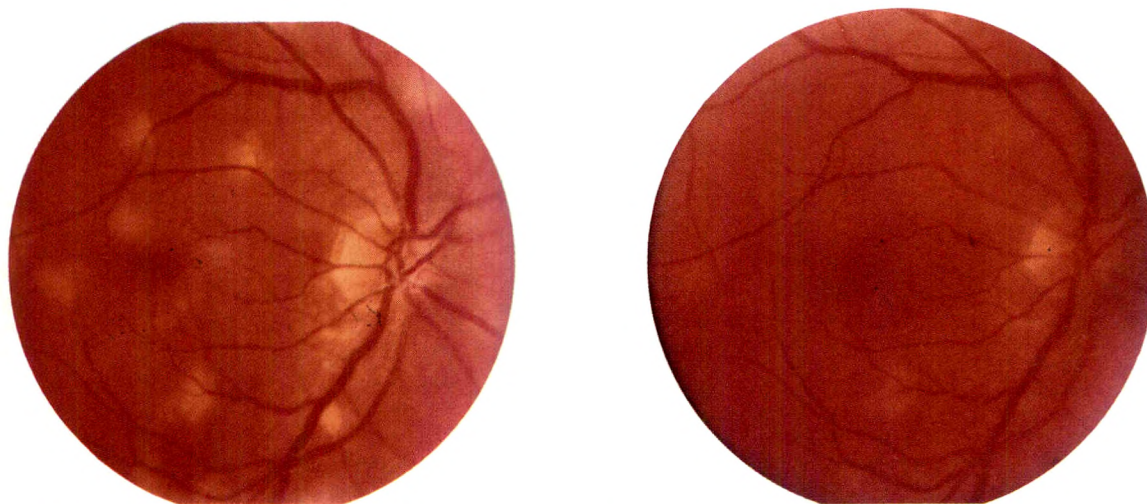
Fig. 1 (Dugel and associates). Case 1. Right eye on initial examination (left) and five months after treatment (right).
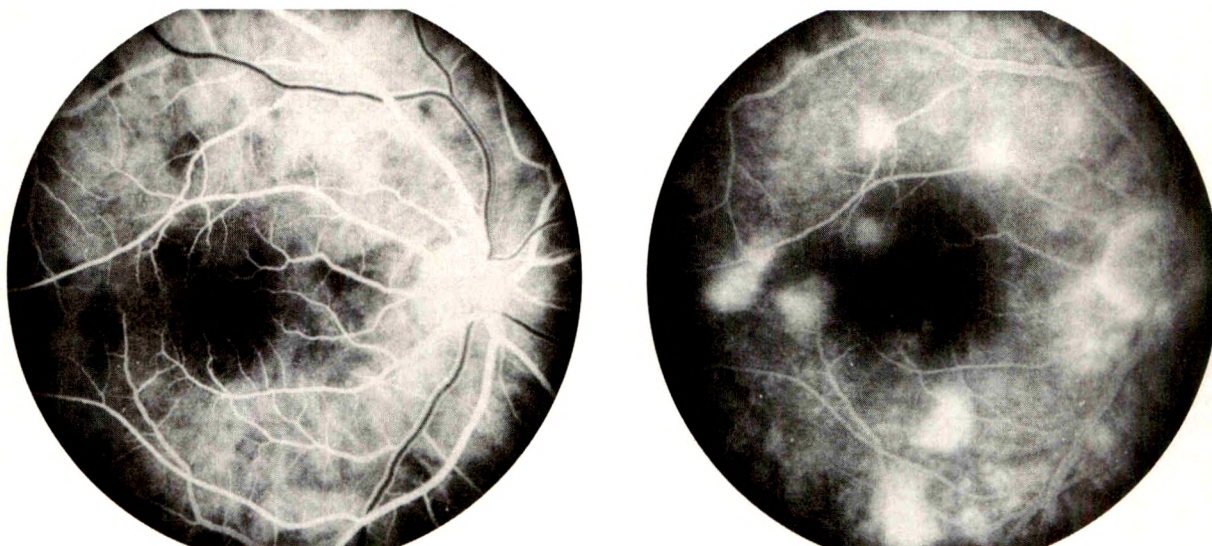
Fig. 2 (Dugel and associates). Case 1. Fluorescein angiogram of the right eye on initial examination shows early choroidal blockage (left) and late staining (right).

rhagic, necrotizing retinitis involving 270 degrees at the equator in the right eye and 90 degrees at the equator in the left eye. There were 20 to 25 yellow-white, round or oval lesions in the posterior pole of each eye at the level of the choroid (Fig. 3, left). The lesions were ⅓ to ½ disk diameter in size, but some were confluent. Results of the remainder of the physical examination were unremarkable.

A presumptive diagnosis of extrapulmonary *P. carinii* infection was made, and the patient was hospitalized for a three-week course of intravenous ganciclovir (10 mg/kg of body weight per day) and pentamidine (4 mg/kg of body weight per day). An extensive examination, including chest radiographs, an arterial blood gas test, liver function tests, and abdominal computed tomography, showed no abnormalities. The patient was followed up by monthly fundus photographs and fluorescein angiograms, and after 12 weeks most of the yellow-white lesions had disappeared, leaving no overlying pigmentary change (Fig. 3, right). The remaining lesions were smaller and with
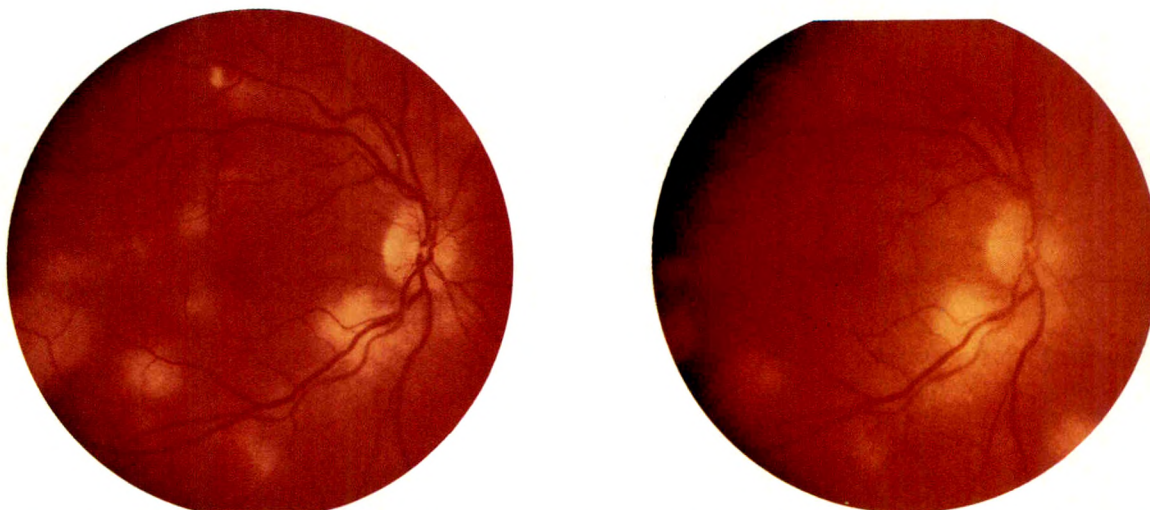
Fig. 3 (Dugel and associates). Case 2. Right eye on initial examination (left) and three months after treatment (right).

sharper borders, and there was slight granularity of the overlying retinal pigment epithelium. The patient subsequently gained 10 pounds and remained without any extraocular symptoms five months later.

Discussion

The characteristic ocular manifestations of disseminated *P. carinii* infection were reported by Rao and associates,[5] who described three patients with AIDS who had multifocal, white, choroidal lesions identical to those of our patients. In each of their patients, *P. carinii* was identified in the choroid by histologic and electron microscopic studies at postmortem examination. Extensive dissemination involving the lung, heart, pancreas, gastrointestinal tract, liver, spleen, lymph nodes, bone marrow, adrenal glands, and thyroid was found in each of the three patients.

Based on this previous report, it is reasonable to assume that both of our patients may have had extrapulmonary dissemination not only to the choroid but to visceral organs. Although *P. carinii* infection in humans is usually limited to the lungs, organisms have been detected outside the extracellular space in the pulmonary parenchyma as well as in various viscera. Twenty-one patients with previously diagnosed AIDS and subsequent extrapulmonary *P. carinii* infection have been described.[5-20] Most of these patients were treated successfully because the diagnosis was made in the early stages of the disease. Most patients who were not diagnosed early died. This underscores the importance of the ophthalmic examination, as ocular changes may be the initial manifestation of disseminated disease, even in patients who appear to be healthy.

The United States Public Health Service recommends that all patients with previous *P. carinii* pneumonia receive either trimethoprim and sulfamethoxazole or aerosolized pentamidine for prophylaxis against recurrent infection. A serious disadvantage of long-term aerosolized pentamidine therapy is that, although local prophylaxis may suppress *P. carinii* infection sufficiently in the lungs to prevent recurrence of pneumonia, this treatment may be insufficient to prevent reactivation of organisms that disseminated presumably outside the lungs before prophylaxis. We believe that ophthalmic manifestations may be the only early sign of extrapulmonary dissemination in some patients, and recommend that patients treated with long-term aerosolized pentamidine undergo periodic ophthalmologic examinations.

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OPHTHALMIC MINIATURE

I had to lean against his cradle, counting on its rockers for support. Because see, darling, here they were. The same. The eyes—old and young all mixed in them, those eyes I'd first seen peeking (civilian) from the Captain's fort of a face. Now my boy batted his lashes, showing this 20/20 sweetness . . . . Just when I thought I would never reach the boy I'd first spied hid so deep in the smug reviewing-stand officer, just when my own tiredness made each dawn feel like a huge new horizontal subtraction mark, I looked down at my child's blue blankets, I saw he'd torn that whole set of eyesight free from trouble.

Allan Gurganus, *Oldest Living Confederate Widow Tells All*
New York, Alfred A. Knopf, 1989, p. 324

The Natural Course of Central Retinal Vein Occlusion

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Patrick Mardesich, M.D., and Cheryl Enger, M.S.

We reviewed the records of 160 patients who had central retinal vein occlusion between 1980 and 1985. Of 168 eyes, 107 (64%) were classified as nonischemic types and 61 (36%) were classified as ischemic types. Of 107 nonischemic eyes, ten (9%) converted to the ischemic variant. Of 107 nonischemic eyes, 33 (31%) lost three or more lines of visual acuity irrespective of initial visual acuity. A final visual acuity less than or equal to 20/200 was recorded in 57 of 61 (93%) of ischemic eyes and 53 of 107 (50%) of nonischemic eyes.

CENTRAL RETINAL VEIN OCCLUSION may result in permanent, severe, visual impairment. We reviewed the records of all patients examined at the Retinal Vascular Center of the Wilmer Institute between January 1980 and December 1985 who had a diagnosis of central retinal vein occlusion to learn more of the history of this disease and to identify various risk factors and prognostic indicators.

Patients and Methods

We selected patients on the basis of an unambiguous diagnosis of central retinal vein occlusion documented by fundus photography and fluorescein angiography. The characteristic criteria were as follows: scattered intraretinal hemorrhages, venous dilatation, and tortuosity in all quadrants centered on the disk; optic disk swelling; and delayed arteriovenous filling (> 15 seconds). Two independent, masked observers (P.M.Q. and M.J.E.) classified the fluorescein angiograms and color photographs of all eyes with central retinal vein occlusion as either ischemic or nonischemic. Disputed cases were jointly adjudicated. The features of ischemic central retinal vein occlusion were five or more contiguous disk areas of capillary nonperfusion, leakage or staining of any venule wall, or evidence of retinal or anterior segment neovascularization. Thus, by definition, all eyes with neovascularization at baseline were assigned to the ischemic group. We classified eyes with central retinal vein occlusion without any of these features at baseline examination as nonischemic. This system was weighted to place questionably ischemic eyes in the ischemic group. Conversion from the nonischemic type to the ischemic type was defined by either development of retinal or anterior segment neovascularization or development of fluorescein angiographic changes of ischemia.

We reviewed the patients' medical histories, present illnesses, and medications currently used. If patients stated they had high blood pressure or were using an antihypertensive medication, they were considered to have systemic hypertension.

We excluded patients who received photocoagulation before their first visit to the Retinal Vascular Center because we could not always verify the indications for such treatment. We included patients we treated with panretinal photocoagulation for retinal or anterior segment neovascularization, however, since this treatment represents the accepted standard of care for these patients. Where recent ophthalmic follow-up was inadequate, we contacted the referring ophthalmologist to provide current clinical information regarding visual acuity and the presence of neovascularization. Patients with less than six months of follow-up were excluded.

Group comparisons were performed by using the chi-square test for independence. Kaplan-

Meier experimental survival analysis[1] was used to estimate cumulative risks over time. Change in visual acuity was measured according to visual acuity on a modified Bailey-Lovie chart by using the logmar technique.[2]

Results

A total of 226 eyes with central retinal vein occlusion were identified. Of these, 58 were excluded because of previous laser treatment (14 eyes), less than six months of follow-up (19 eyes), or ungradable baseline photographs (25 eyes). We studied a total of 168 eyes from 160 patients. Of these, 61 eyes (36%) were ischemic and 107 (64%) were nonischemic at the initial visit. Of the 160 patients, the mean age was 63 years (range, 14 to 93 years). Eighty-nine were male (56%) and 71 were female (44%). Of 168 eyes, 82 were right eyes (49%) and 86 were left eyes (51%). The eyes were affected bilaterally in 16 patients. Follow-up ranged from six months to six years (mean, 22 months). Age, sex, race, and bilateral occurrence were not related to the severity of venous occlusion.

Ten eyes with central retinal vein occlusion (9%) were converted from the nonischemic to the ischemic type between one and 36 months after the initial visit (median, eight months). No significant ophthalmic or systemic risk factor was identified in the converted group when compared to eyes remaining nonischemic.

Of the 160 patients, 24 were under 50 years of age (16 males and eight females). Of these patients, the right eye was involved in eight cases and the left in 16 cases. Ten of these eyes were ischemic, two converted to the ischemic type, and 12 remained nonischemic. We compared the prevalence of systemic diseases in young and old patients (Table 1). Of young patients 13 (54%) compared to 40 (29%) of older patients had no identified systemic disorder (P = .02). Three (13%) of the young patients had a collagen vascular disorder compared to three (2%) in the older group (P = .01). None of the young patients had cardiovascular disease (P = .003) or cerebrovascular disease (P = .12). Ten (42%) of the young patients had hypertension (P = .15) compared to 78 patients (57%) in the older age group.

At the time they were first examined at Wilmer, 25 patients had retinal vascular occlusive disease in the fellow eye. Of these patients, 16 had central retinal vein occlusion, eight had branch retinal vein occlusion, and one had branch retinal artery occlusion. During the course of this study only one additional patient developed a branch retinal vein occlusion in the fellow eye. No other vascular occlusions in the fellow eye were noted during follow up. We failed to find any significant systemic risk factors associated with bilateral retinal vascular occlusive disease. Similarly, when comparing 134 patients who had central retinal vein occlusion in one eye only to 11 patients who had a history of central retinal vein occlusion in one eye and were examined by us to have central retinal vein occlusion in the fellow eye, the severity of disease in the examined eyes, complication rate, and visual outcome were similarly distributed in both groups. The numbers, however, were small in this subgroup.

Baseline visual acuity in the nonischemic group varied from 20/15 to counting fingers (Fig. 1). In the nonischemic group, a final visual acuity of 20/200 or less was noted in six of the 28 eyes (21%) with initial visual acuity better than or equal to 20/40, and in 30 of the 34 eyes (88%) with initial visual acuity less than or equal to 20/200. Only 16 of 107 nonischemic eyes (15%) gained three or more lines of visual acuity from baseline, whereas 33 eyes (31%) lost three or more lines of visual acuity (Table 2). Overall, the poorer the initial visual acuity, the poorer the visual prognosis (chi-square for trend, P < .001). Of the 107 eyes in the nonischemic group, 53 (50%) had a final visual acuity less than or equal to 20/200; only six (6%) resolved with visual acuity, ophthalmoscopic, and angiographic features returning to normal

TABLE 1

A COMPARISON OF SYSTEMIC DISEASE AND AGE IN 160 PATIENTS

SYSTEMIC DISEASE	PATIENTS < 50 YEARS OF AGE (NO. = 24) NO. (%)	PATIENTS ≥ 50 YEARS OF AGE (NO. = 136) NO. (%)	P VALUE
Diabetes	2 (8)	25 (18)	.230
Hypertension	10 (42)	78 (57)	.150
Cardiovascular disease	0 (0)	44 (32)	.003
Cerebrovascular disease	0 (0)	18 (13)	.120
Collagen vascular disorders	3 (13)	3 (2)	.010
No systemic disease	13 (54)	40 (29)	.020
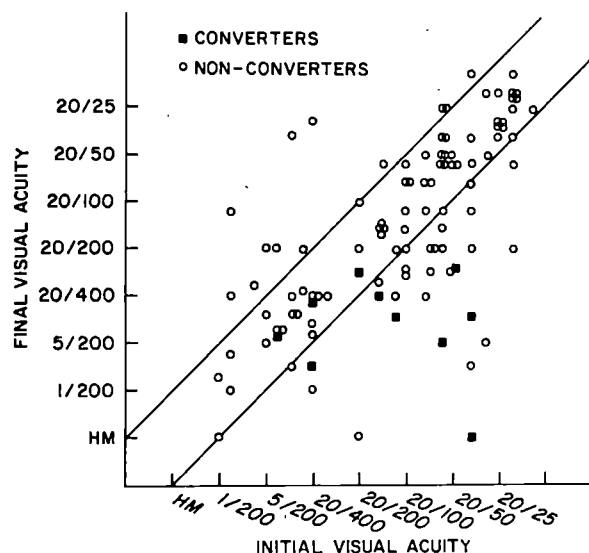
Fig. 1 (Quinlan and associates). Scatter plot of initial vs final visual acuity in nonischemic eyes (HM indicates hand motions).

within six months of the original event. All of these eyes had incurred a mild central retinal vein occlusion with initial visual acuity better than or equal to 20/30. Of the remaining 101 nonischemic eyes, ten (10%) converted to the ischemic type of central retinal vein occlusion, and 91 (90%) remained nonischemic.

The initial visual acuity was variable in the ten eyes that converted from the nonischemic to the ischemic type of central retinal vein occlusion, ranging from 20/20 to counting fingers (Fig. 1). In all cases of conversion, the visual acuity was worse than 20/200; six eyes (60%) had a final visual acuity of counting fingers or less, and one eye had a visual acuity of hand motions.

All eyes in the ischemic group had a baseline visual acuity of 20/100 or less (Fig. 2). Eleven eyes had initial or final visual acuities that could not be measured on a visual acuity chart.

Of the remaining 50 ischemic eyes, 14 (28%) improved three or more lines visual acuity from baseline (Table 2). Of 61 ischemic eyes, 57 (93%) had a final visual acuity less than or equal to 20/200, 33 (54%) were counting fingers or less, and 22 (36%) had a final visual acuity of hand motions or less. However, two eyes with initial visual acuity of 20/100 did recover visual acuity of 20/80.

Forty-two of the 71 ischemic or converted eyes developed anterior segment (iris or angle) neovascularization. Of these, 30 had anterior segment neovascularization at initial examination. The remaining 12 eyes without anterior segment neovascularization at initial examination all developed anterior segment neovascularization within 36 months of the original event (median, four months); Kaplan-Meier experimental survival curve shows that three (25%) developed anterior segment neovascularization after one year (95% confidence intervals, 10% to 40%) and four (35%) after two years.

Retinal neovascularization or vitreous hemorrhage developed in 21 of the 71 ischemic or converted eyes. Combined vitreous hemorrhage and retinal neovascularization occurred in 13 eyes, retinal neovascularization alone in four eyes, and vitreous hemorrhage alone in four eyes. Six eyes had retinal neovascularization at baseline; the other 15 developed it within 36 months (median, five months). Three of these eyes had converted to the ischemic type of central retinal vein occlusion. Eyes remaining nonischemic did not develop retinal neovascularization or vitreous hemorrhage.

Thirteen of 42 eyes (31%) with anterior segment neovascularization also had retinal neovascularization or vitreous hemorrhage (combined vitreous hemorrhage and retinal neovascularization in nine, retinal neovascularization alone in one, and vitreous hemorrhage alone in three). Conversely, 13 of the 21

TABLE 2
CHANGE IN TOTAL LINES OF VISUAL ACUITY FROM BASELINE VISIT

	NONISCHEMIC EYES (NO. = 107) NO. (%)	ISCHEMIC EYES (NO. = 50) NO. (%)	ALL EYES WITH CENTRAL RETINAL VEIN OCCLUSION (NO. = 157)* NO. (%)
Gained 3 or more lines	16 (15)	14 (28)	30 (19)
Stable with 3 lines	58 (54)	24 (48)	82 (52)
Lost 3 or more lines	33 (31)	12 (24)	45 (29)

*Total number of eyes does not include 11 eyes that did not have measurable vision on a visual acuity chart.

eyes (62%) with retinal neovascularization, vitreous hemorrhage, or both, had concomitant anterior segment neovascularization.

Fifty patients started aspirin therapy at the time the central retinal vein occlusion was first diagnosed. Of these, 21 patients were ischemic, 28 were nonischemic, and one converted from nonischemic to ischemic while on aspirin therapy. There was no significant association between prognosis and aspirin therapy, but the numbers were small in this subgroup.

Forty-two ischemic eyes were treated with panretinal photocoagulation. Three eyes received panretinal photocoagulation prophylactically and 39 eyes received panretinal photocoagulation for the treatment of anterior segment neovascularization, retinal neovascularization, or both.

Of 61 eyes, 31 (51%) in the ischemic group and 49 of 107 eyes (46%) in the nonischemic group developed disk collaterals. Collaterals were not related to an improvement in visual acuity. Macular pigment change resulting from chronic cystoid macular edema or foveal blood was noted in 54 of 61 eyes (89%) in the ischemic group and 79 of 107 eyes (74%) in the nonischemic group and was not associated with visual outcome.

Discussion

Our findings parallel those reported previously in many areas such as anterior segment neovascularization; however, the visual prognosis in our series was poorer than previous studies. Hayreh[3] reported that nonischemic central retinal vein occlusion (venous stasis retinopathy) was a benign and self-limited condition. Zegarra, Gutman, and Conforto[4] reported that eight of ten (80%) nonischemic eyes had a final visual acuity of 20/60 or better. Those eyes with a visual acuity less than 20/60 had converted to the ischemic type of central retinal vein occlusion with an unfavorable outcome. In our study, good initial visual acuity provided no guarantee of a satisfactory visual outcome. In the nonischemic group, baseline visual acuity varied from 20/20 to hand motions; 33 (31%) of eyes lost three or more lines of visual acuity from baseline. Of nonischemic eyes 64 (60%) had a visual acuity worse than 20/80; 53 eyes (50%) that initially had the nonischemic type became legally blind (visual acuity of 20/200 or worse).
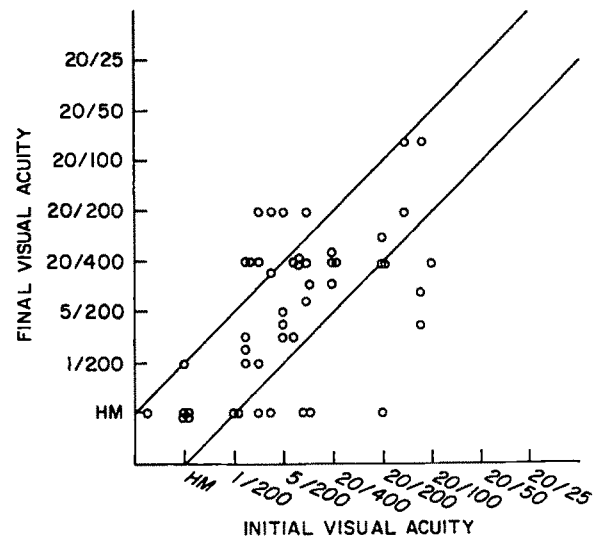
Fig. 2 (Quinlan and associates). Scatter plot of initial vs final visual acuity in ischemic eyes (HM indicates hand motions).

Baseline visual acuity in all ischemic eyes was 20/100 or less. Fifty-seven (93%) ischemic eyes had a final visual acuity less than or equal to 20/200, which indicates that visual recovery was unlikely in this group. However, two ischemic eyes (3%) did recover visual acuity to 20/80. Zegarra, Gutman, and Conforto[4] showed similar results. In their study, 14 of 17 ischemic eyes (82%) had a final visual acuity of 20/400 or less.

The distribution of nonischemic to ischemic cases is comparable to Hayreh's previous results.[3] However, the distribution of ischemic compared with nonischemic eyes is not population-based and may reflect a referral bias to a tertiary care center. It is possible that many of our patients were referred because of decreasing vision or the onset of neovascular complications.

Ten nonischemic eyes (9%) converted to the ischemic type of central retinal vein occlusion. Considering that most of our patients are seen by referral, it is possible that many of the ischemic patients represent converters, those who started with the nonischemic type but converted to the ischemic type before examination at Wilmer. Thus, the true prevalence of conversion may be higher than indicated here. Conversion occurred at a median of eight months after first being seen at Wilmer. Once converted to the ischemic type, eyes assumed the characteristics of the ischemic group with the same poor visual prognosis and incidence of complications. Those who converted did not

have any greater prevalence of systemic disease or any features that could help predict conversion. Whereas Minturn and Brown[5] found that poor initial visual acuity was related to conversion, we found that the initial visual acuity in these eyes varied and was not helpful in predicting conversion.

When we compared the bilateral to the unilateral cases, the prevalence of diabetes, hypertension, and cardiovascular disease did not vary between the two groups. The overall distribution of systemic disease was not more marked in patients with bilateral vascular occlusive disease. When comparing the second eyes of patients with bilateral central retinal vein occlusion to the unilateral eyes, the prognosis for disease severity, visual outcome, and complication rate was the same.

Nearly half of the patients under 50 years of age had a treatable systemic disorder. Considering that hypertension is more prevalent in the elderly, we were surprised that ten (42%) patients under 50 had hypertension. Three (13%) young patients had a collagen vascular disorder compared to three (2%) in the older group (P = .01). This may explain reports of a positive response to corticosteroid treatment in younger patients with central retinal vein occlusion. Although Zegarra, Gutman, and Conforto[4] and Green and associates[6] questioned the contribution of the use of oral contraceptives in young females to the development of central retinal vein occlusion, none of the eight female patients under 50 years of age were taking oral contraceptives either before or at the time of the central retinal vein occlusion.

Anterior segment neovascularization, which leads to neovascular glaucoma, has been reported in 16% to 67% of all eyes with central retinal vein occlusion, usually within 90 days.[7-19] Anterior segment neovascularization was noted in our patients within a median of four months after initial examination. Most of our patients with anterior segment neovascularization had this finding at the initial examination (30 of 42 eyes, 71%). However, ischemic eyes remained at risk for anterior segment neovascularization even three years later. These figures represent conservative estimates. Anterior segment neovascularization likely develops sooner than indicated by this study.

We observed retinal neovascularization in 21 of 71 ischemic or converted eyes (30%). Of these, 13 eyes (62%) with retinal neovascularization, vitreous hemorrhage, or both also had anterior segment neovascularization. Conversely, 13 of 42 eyes (31%) with anterior

segment neovascularization had concomitant retinal neovascularization, vitreous hemorrhage, or both. Similarly, Magargal and associates[18] reported disk neovascularization in nine of 29 eyes (31%) with neovascular glaucoma. Trempe, Takahashi, and Topilow[19] suggested that retinal neovascularization will not develop in the presence of a posterior vitreous detachment. In histopathologic studies, Chan and Little[20] found retinal neovascularization in only one of ten eyes enucleated for neovascular glaucoma. They postulated that hypoxia destroys retinal capillary endothelial cells, which renders them incapable of neovascular budding and proliferation. Although breakthrough vitreous hemorrhage can occur in the absence of retinal neovascularization, retinal neovascularization must be suspected whenever vitreous hemorrhage is present.

Mieler and Blumenkranz[21] demonstrated a 25% risk of vascular occlusion to the fellow eye in their five-year study of 120 patients. In our study, the prevalence of fellow eye involvement was considerably less. Twenty-five (16%) of our patients had bilateral vascular occlusive disease. Over the five-year study period only one patient developed a vascular occlusion in the fellow eye. Our average follow-up, however, was shorter.

Priluck, Robertson, and Hollenhorst[22] questioned an association between the presence of disk collaterals with an improved visual outcome. They also associated derangement of the macular pigment with a poor visual prognosis. In our study, disk collaterals were not related to central retinal vein occlusion type or an improvement in visual acuity. Although we noted macular pigmentary disturbance in most eyes, it was not associated with a poor visual outcome.

Currently, no treatment exists that has been shown to definitively improve vision in central retinal vein occlusion. The poor visual outcome in central retinal vein occlusion supports consideration of an aggressive therapeutic approach aimed at clot lysis, restoration of blood flow, and improvement in vision. Evaluation of thrombolytic therapy with tissue plasminogen activator is in progress.

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Diagnostic Clinical Findings of a New Syndrome With Night Blindness, Maculopathy, and Enhanced S Cone Sensitivity

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We studied eight patients who had night blindness, maculopathy (often cystoid), degenerative changes in the region of the vascular arcades, relatively mild visual field loss, and an unusual but characteristic electroretinogram. The dark-adapted electroretinogram showed no response to low-intensity stimuli that normally activate the rods, but large, slow responses to high-intensity stimuli. These large, slow waveforms persisted without change under light adaptation, and showed a striking mismatch to photopically balanced short and long wavelength stimuli (with sensitivity much greater to short than long wavelengths). Since there is evidence from other studies that the electroretinogram and psychophysical responses represent hypersensitivity of short wavelength-sensitive (S or blue) cones, we propose that this disorder be called the enhanced S cone syndrome. There can be different degrees of severity in this syndrome, and progression appears to be slow.

A RETINAL DISEASE associated with night blindness, maculopathy (often cystoid), and an unusual pattern of electroretinographic findings in which scotopic and photopic waveforms look similar has been reported.[1-6] Psychophysical, electroretinogram, and fundus reflectometric analyses of photoreceptor-mediated dysfunction in three patients with this disorder indicated that there was severe rod sensitivity loss throughout the retina, no measurable rhodopsin, midspectral cone system abnormalities, and enhanced sensitivity of the short wavelength-sensitive (S or blue) cone system.[7]

The previous reports of this syndrome have described isolated patients, under different diagnostic categories, and have not recognized the unifying clinical features. We have studied eight patients, showing the spectrum of ophthalmoscopic findings that are associated with this disease and defining the diagnostic set of electroretinogram responses that distinguish it from other retinal disorders.

Patients and Methods

We studied eight patients. Patients with large-amplitude electroretinograms (> 300 μV) to conventional high-intensity stimuli are listed first in the Table (Cases 1 through 5), followed by those with smaller electroretinogram amplitudes (Cases 6 through 8). All of the patients were in good general health. Although the patients were studied in different laboratories, the electroretinogram recording techniques were similar in principle.[8-11] Contact lens electrodes were used, and either a ganzfeld stimulator dome (United States) or a Henkes diffuser electrode (Germany) was used to produce a full-field stimulus.

Results

The common symptom among these patients was night blindness, which all patients reported they had had for as long as they could remember. There were no complaints of color or side vision loss except for the oldest patient (Case 8), who had some peripheral vision disturbances. The family history was noncontributory in all patients except one (Case 4), who had a brother with similar symptoms. None of the families were aware of parental consanguinity. Visual acuity was reduced for many patients, but the onset and severity were variable. There was no characteristic refractive error.

The fundus appearance in this syndrome (Figs. 1 to 4) was symmetric between the two eyes and characterized by degenerative changes in the region of the vascular arcades. The lesions ranged from yellow flecks that sometimes resembled drusen to pigment epithelial atrophy and a deposition of black pigment spots. The far periphery was normal or showed only mild granularity. The central macula was abnormal in all cases, ranging from loss of the foveal reflex in some patients (Fig. 1) to cystoid degeneration of the fovea in others (Figs. 2, 3, and 4). However, angiograms done on five of the patients showed no leakage of dye associated with the cystoid changes (Figs. 3 and 4). One

patient (Case 5) developed subretinal neovascularization in one eye. The optic disks were normal; the vessels were of normal caliber or only slightly narrowed.

Four patients (Cases 3, 4, 6, and 7) have been followed up for a minimum of four (and as long as 12) years, during which time two patients lost visual acuity (Cases 4 and 5) and the pigmentary changes in the arcade region became more prominent but not much more extensive. There was some intensification of the degenerative lesions over time, but little increase in the area of involvement (Fig. 3). The electrophysiologic measures have not shown a clear pattern of progression over time, and the electroretinogram b-wave amplitudes were mostly stable in these patients.

Dark adaptation was universally impaired among these patients. Conventional dark adaptation curves showed a normal initial cone limb, but little or no rod adaptation beyond the cone threshold (Fig. 5). Three patients (Cases 1, 2, and 8) demonstrated a small amount of slow, additional recovery of sensitivity (0.5 to 0.7 log unit over 60 to 90 minutes).[7]

The visual fields showed varying degrees of midperipheral scotomas (Fig. 6). Patients with only drusenlike or flecklike arcade lesions generally had normal kinetic fields (for example, with a Goldmann perimeter), whereas those with more advanced degenerative changes had relative ring scotomas.
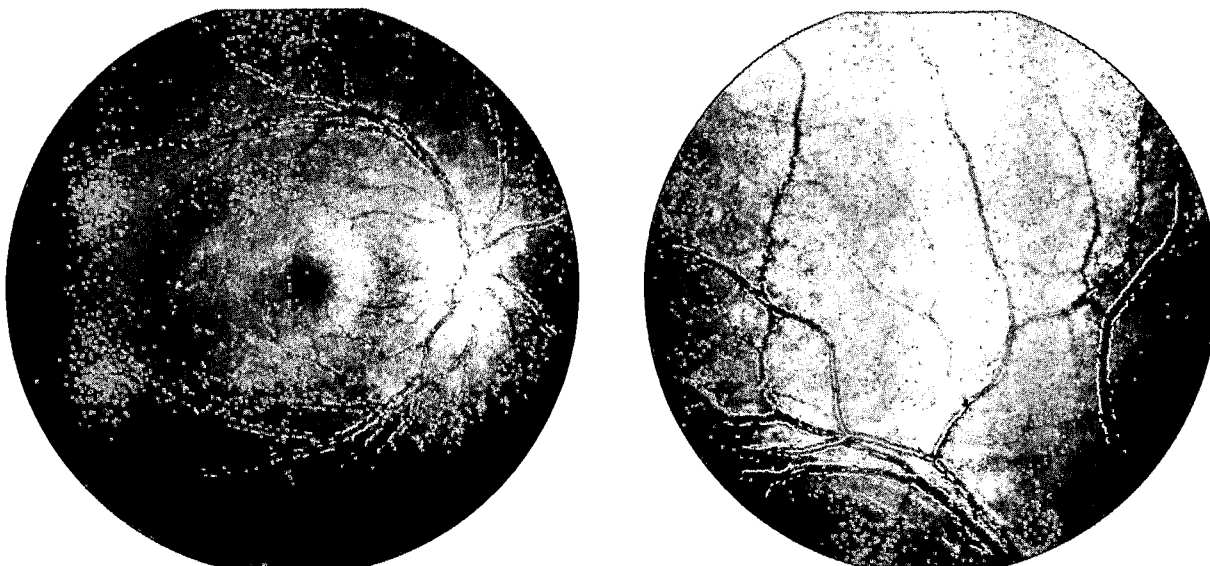
Fig. 1 (Marmor and associates). Case 1, the youngest in our series, had the mildest fundus lesions and the largest electroretinogram responses. Left, Wide-angle photograph showing faint yellow spots scattered in a ring in the vascular arcade region. The macula is dull. Right, Superotemporal arcade of the same eye, showing the faint yellow lesions.

TABLE
CLINICAL CHARACTERISTICS OF EIGHT PATIENTS

PATIENT NO., AGE (YRS), SEX	ARCADE REGION	FOVEA	FLUORESCEIN LEAKAGE*	REFRACTIVE ERROR†	VISUAL ACUITY R.E.	VISUAL ACUITY L.E.	VISUAL FIELDS‡
1, 10, F	Yellow flecks	Dull	—	−0.50	20/25	20/20	Full
2, 28, M	Pigmentary degeneration	Cystoid	None	+1.50	20/60	20/200	Relative ring scotoma
3, 12, M	Flecks	Dull	—	+4.00	20/30	20/25	Full
16	Same	Same	—	+4.00	20/30	20/60	Same
4, 23, M	Flecks	Cystoid	None	0	20/200	20/200	Central scotoma
28	Pigmented flecks	Same	—	0	20/200	20/200	Same
5, 23, M	Depigmented flecks	Scar, R.E. Cystoid, L.E.	—	+2.50	20/200	20/200	Central scotoma
25	Same	Same	—	+2.50	20/200	20/200	Same
6, 7, M	Pigmentary degeneration	Dull	—	0	20/30	20/25	—
15	Same	Same	None	−0.25	20/50	20/30	Relative ring scotoma
19	Same	Same	—	−1.75	20/30	20/25	Same
7, 9, F	Yellow flecks	Dull	—	+0.75	20/20	20/20	—
12	Flecks and gray depigmentation	Cystoid	—	−0.50	20/40	20/40	—
17	Pigmentary degeneration	Cystoid with hole	None	−0.50	20/40	20/40	Relative ring scotoma
19	Same	Same	—	−0.75	20/50	20/60	Same
8, 28, F	Not available	Cystoid, R.E. Scar, L.E.	—	—	20/20	20/200	—
40	Yellow flecks	Same	None	+4.50	20/50	20/200	Relative ring scotoma

*Refers to the presence or absence of late foveal leakage (cystoid edema).
†Spherical equivalent, average of the two eyes.
‡Goldmann or equivalent kinetic perimetry.
§Farnsworth D-15 test for all patients except one (Case 7), who was tested with Hardy-Rand-Rittler plates.
‖In response to the conventional high-intensity stimulus under dark-adapted (scotopic) or light-adapted (photopic) conditions.

Color vision was consistently normal by testing with the Farnsworth D-15 panel or Hardy-Rand-Rittler plates.

Conventional electroretinogram testing of these patients showed striking results (Fig. 7). In the dark-adapted state, there was no response to dim stimuli but a substantial response to brighter stimuli. The scotopic waveforms showed little diminution or change in the presence of routine levels of background illumination that are used to isolate cone responses,[8] and they were strikingly different from a typical cone response. The light-adapted b-wave implicit time, for example, was in the range of 60 milliseconds, roughly twice the normal time. The response in these patients was characterized by an unusually large and prolonged initial negativity (a-wave), especially at high stim-

TABLE (Continued)
CLINICAL CHARACTERISTICS OF EIGHT PATIENTS

COLOR[j]	ELECTRO-OCULOGRAM	ELECTRORETINOGRAM B-WAVE (μV)[l]	
		SCOTOPIC	PHOTOPIC
Normal	1.8	475	475
Normal	—	350	300
Normal	1.1	420	380
—	—	420	380
—	1.5	345	230
—	—	345	230
Normal	1.15	400	315
—	—	400	315
Unreliable	—	150	75
Normal	—	100	50
—	—	150	100
—	—	273	127
—	—	208	164
Normal	1.15	210	154
Normal	—	183	139
—	—	—	—
Normal	—	100	80

ulus intensities. The response to 30-Hz flicker was reduced in all patients, ranging from 60 μV (Case 1) to nonrecordable. Oscillatory potentials were recordable in only a few patients (Cases 1 and 2).

These patients comprised two groups. In the first group (Cases 1 through 5), the maximal electroretinogram responses were large, falling within or close to the normal range of scotopic

Fig. 2 (Marmor and associates). Case 2, central macula exhibiting prominent cystoid degeneration. There was no leakage on fluorescein angiography.

electroretinogram amplitudes. These patients showed extraordinarily large electroretinograms under light-adapted conditions. In the second group (Cases 6 through 8), scotopic electroretinogram amplitudes were reduced but the photopic signals were still homologous and remarkable for their slow waveform if not for their amplitude.

The electroretinogram responses to stimuli of increasing intensity had several unique characteristics. In a typical series of recordings with normal responses for comparison, the responses of the patients developed a large broad a-wave and remained virtually constant with respect to b-wave timing under both photopic and scotopic conditions, whereas normal scotopic responses showed a decrease in b-wave implicit time with increasing stimulus intensity (Fig. 8).

The relationship between electroretinogram response amplitude and stimulus intensity is shown graphically in Figure 9. All of the curves (a- and b-waves, dark- and light-adapted) rise more steeply than normal, and the a- and b-waves are similar. The scotopic electroretinogram of our patients was insensitive to dim light stimuli that normally elicit a rod response, but increased to a large amplitude when higher-intensity stimuli were used. The photopic V-log I curves are similar to those from normal patients at lower intensities, but at higher intensities the amplitudes are larger and the function is steeper. In contrast to normal eyes, none
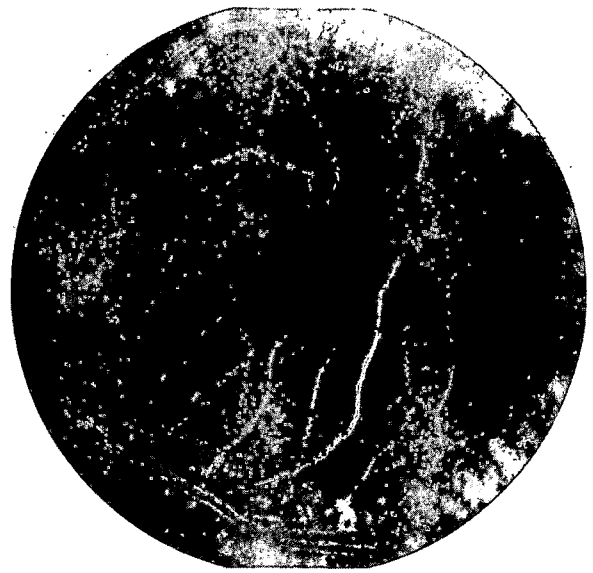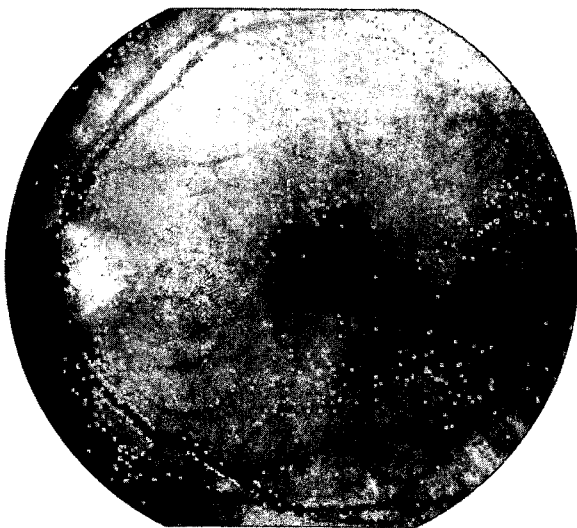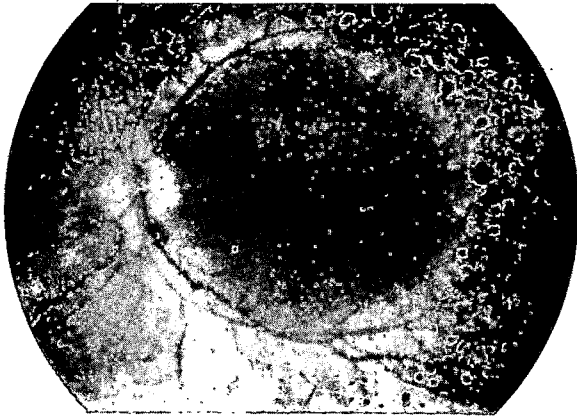
Fig. 3 (Marmor and associates). Case 6. Top left, Wide-angle photograph at age 19 years, showing a prominent ring of retinal degenerative changes in the vascular arcade region. Middle left, Superotemporal arcade of the same eye at 7 years. Middle right, The same arcade region at 15 years, showing little progression over the eight-year period. Bottom left, The central macula at age 15 years lacked foveal reflexes and showed suggestive cystoid changes. Bottom right, Late-phase fluorescein angiogram taken at the same time, showing no leakage.
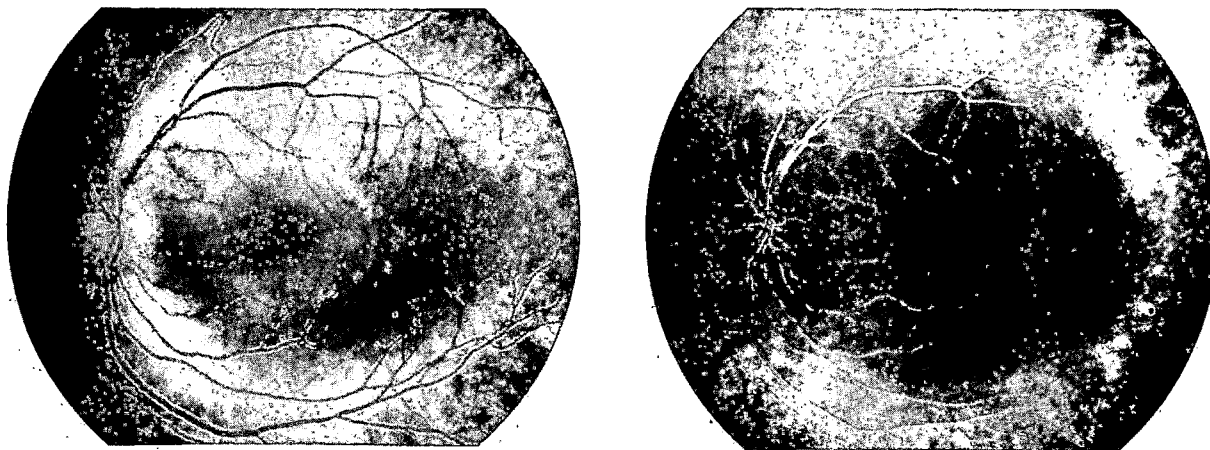
Fig. 4 (Marmor and associates). Case 7. Left, Wide-angle fundus photograph at 17 years, showing a holelike foveal lesion and pigmentary degeneration in the arcade region. Right, Fluorescein angiography shows hyperfluorescence in the degenerated regions, but no foveal leakage.

of the eyes in our series showed a plateau of b-wave amplitude at the highest conventional scotopic or photopic stimulus intensities. The results of presenting brighter stimuli to one patient (Case 6) are shown in Figure 10. Although this patient (Case 6) is in our low-amplitude group, the a-waves and b-waves rose to high amplitudes with bright stimuli that exceeded the intensities used in standard electroretinogram testing.[9] The b-wave eventually reached a plateau, but only at stimulus levels well above normal for both dark- and light-adapted signals. The a-wave did not show a plateau, and exceeded the b-wave in amplitude at the highest scotopic and photopic stimulus intensities.

We observed in four of our patients (Cases 1, 2, 6, and 7) that the single-flash photopic electroretinogram failed to augment during the first ten to 20 minutes of light adaptation, whereas normal cone responses grow substantially.[12] Increasing the background light intensity above $20 \text{ cd} \cdot \text{m}^{-2}$ in two patients (Cases 1 and 6) led to a diminution of the responses (as occurs with normal cones).

Long and short wavelength stimuli, balanced for photopic and scotopic signals, were presented to five of our patients (Cases 1, 2, 6, 7, and 8). The light-adapted responses showed a striking photopic mismatch that is an important diagnostic feature of this syndrome (Fig. 11). The photopic electroretinogram was more sen-
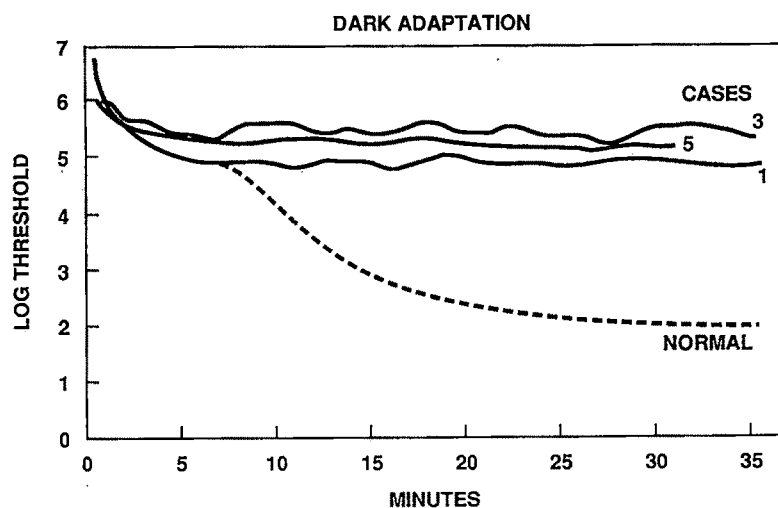
Fig. 5 (Marmor and associates). Representative dark-adaptation curves showing no evidence of rod function within the time frame of conventional dark-adaptation testing.
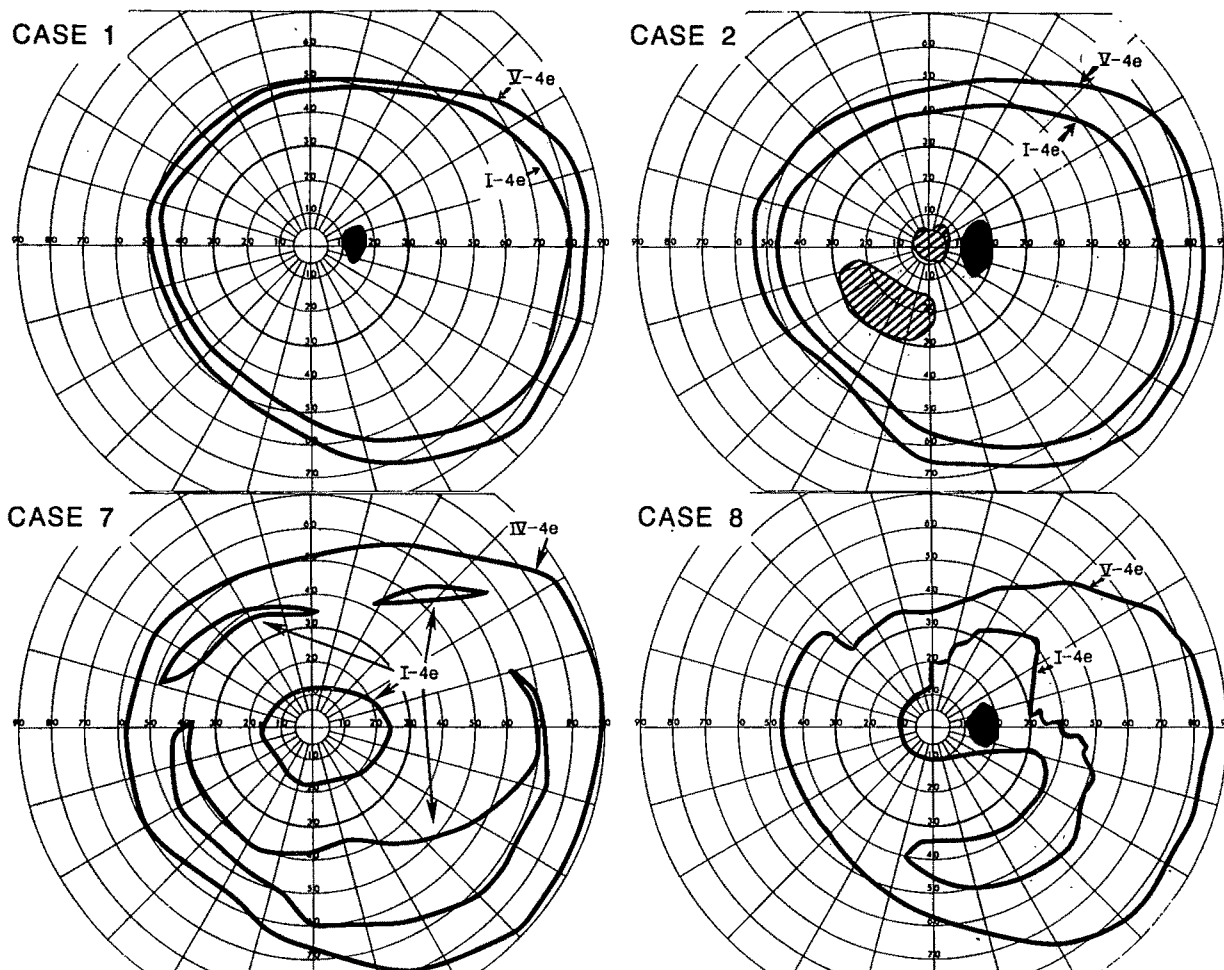
Fig. 6 (Marmor and associates). Representative Goldmann visual fields with defects ranging from none to relative ring scotomas.
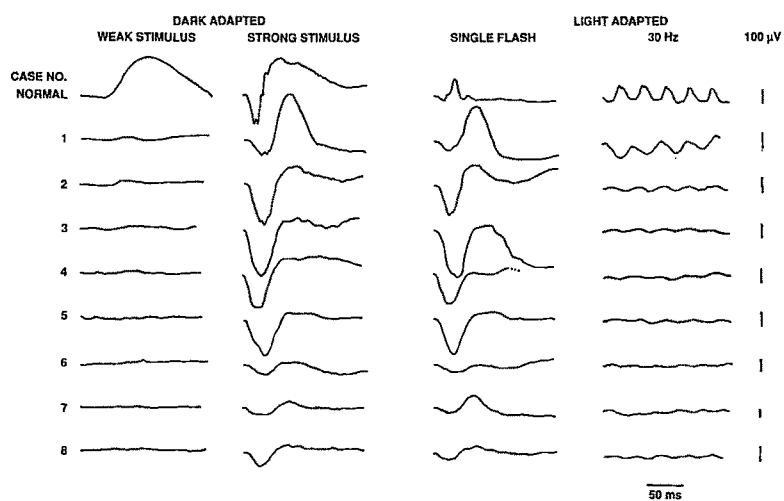
Fig. 7 (Marmor and associates). Electroretinogram tracings from each of our patients exhibit the virtual absence of rod responses and a prominent slow response to bright stimuli that is unaffected by photopic background illumination. Note that the light-adapted electroretinogram amplitudes are much larger than normal for Cases 1 to 5.
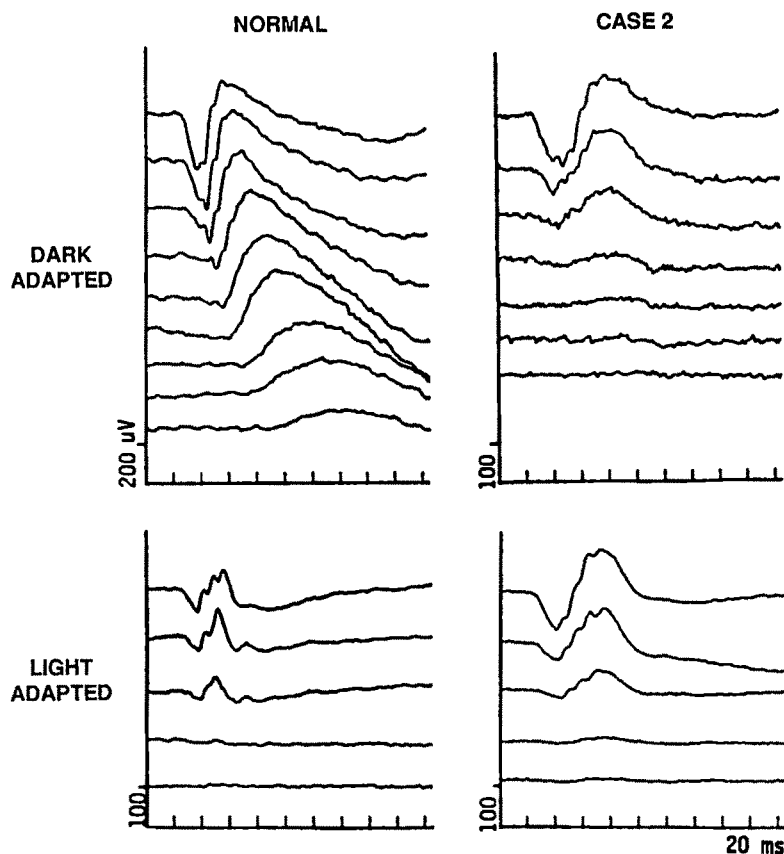
Fig. 8 (Marmor and associates). Case 2, electroretinogram responses arranged to illustrate the change in waveform with increasing stimulus intensity. All of our patients failed to show the normal shortening of the b-wave implicit time.

sitive to blue or green than to red or orange, in contrast to the behavior of normal midspectral cones. The scotopic matches were harder to evaluate and of less diagnostic value under conventional electroretinogram test conditions. Our routine scotopically balanced stimuli produced little response since our patients were insensitive to dim stimuli. The threshold signals were somewhat larger to red than to blue light, perhaps because we elicited a small midspectral cone response.[7]

Electro-oculography performed on several of our patients disclosed light/dark ratios that were reduced but not eliminated. The fast oscillations[18] of the electro-oculograms from two patients (Cases 1 and 7) were subnormal.

Discussion

This group of patients share an unusual but diagnostic set of clinical characteristics: long-standing night blindness and variably reduced visual acuity in association with dull or cystoid maculopathy; retinal degenerative changes in the region of the vascular arcades with relative ring scotomas; absent rod electroretinogram responses (to dim stimuli) but maximal dark-adapted responses that are large and slow, do not saturate with photopic background illumination, and do not reach a plateau of amplitude unless high stimulus intensities are used; and photopic electroretinogram responses that appear nearly identical with the scotopic ones, have an extremely long implicit time (relative to normal cone responses), show a mismatch to photopically balanced short and long wavelength stimuli, and do not augment with light adaptation.

The strikingly supernormal-appearing photopic responses in one subgroup of patients (Cases 1 to 5) are electrophysiologically distinct from those in any disorder of which we are aware. These large photopic signals may also be recognized in some patients who appear to have lower-amplitude responses (Fig. 7) by the use of unusually high-intensity stimuli. Although we are unaware of other conditions that show supernormal photopic responses homologous with scotopic responses, subnormal homologous responses may occur in diseases such
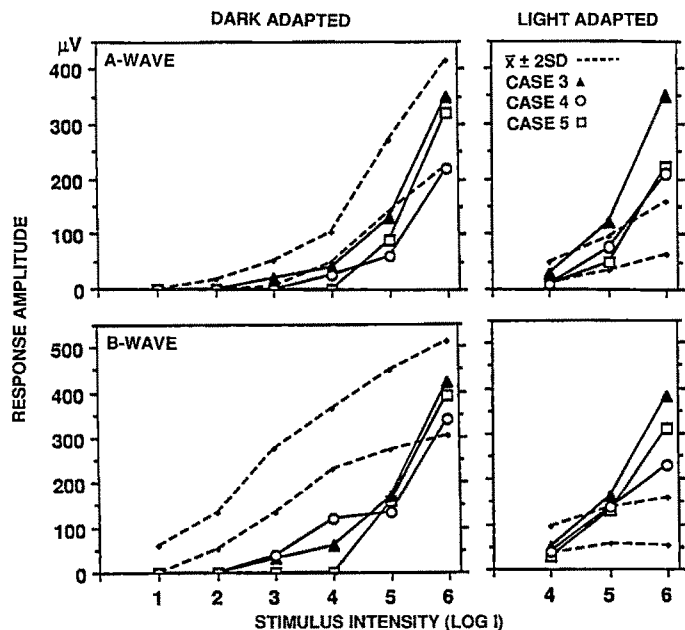
Fig. 9 (Marmor and associates). Representative stimulus-response curves for the a-wave and b-wave of the electroretinogram. Both responses are relatively insensitive to dim stimuli, but the curves rise more steeply than normal as stimulus intensity increases. Stimulus intensity 6 represents 7.8 cd·s·m^{-2}.

as rod-cone dystrophy in which a lack of rod function results in only the cone signal being detectable under both dark- and light-adapted conditions. Differentiation can be made most directly by comparing the light-adapted responses to photopically balanced stimuli. Our

patients show a characteristic mismatch. Some cases previously reported as rod-cone dystrophy with foveal retinoschisis[3] or Goldmann-Favre disease[14] may represent this new syndrome. More severe dystrophies such as retinitis pigmentosa will be distinguished on
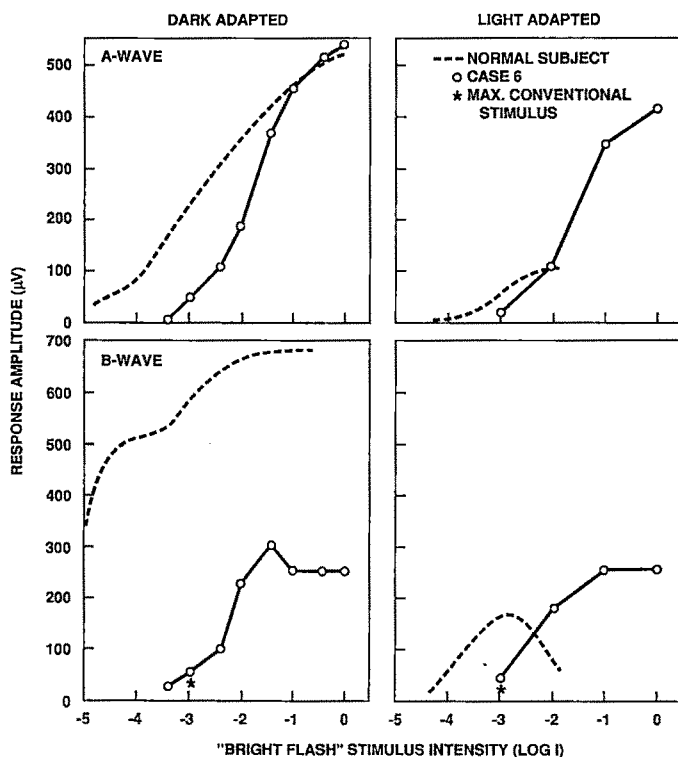
Fig. 10 (Marmor and associates). Case 6, Stimulus-response curves. These responses were generated with a photoflash unit designed to generate bright-flash electroretinograms through opaque media. Our standard maximal stimulus[9] of 3.0 cd·s·m^{-2} is indicated by the asterisk. The a-wave rose continuously with increasing stimulus intensity, but the b-wave reached a plateau about 1.5 log units below the maximal stimulus intensity. Note that the normal photopic b-wave diminishes at high stimulus intensities.

PHOTOPICALLY MATCHED STIMULI

SHORT WAVELENGTH   LONG WAVELENGTH

NORMAL

CASE 2

CASE 6

μV

_| 100

_| 50

_| 100

20 ms
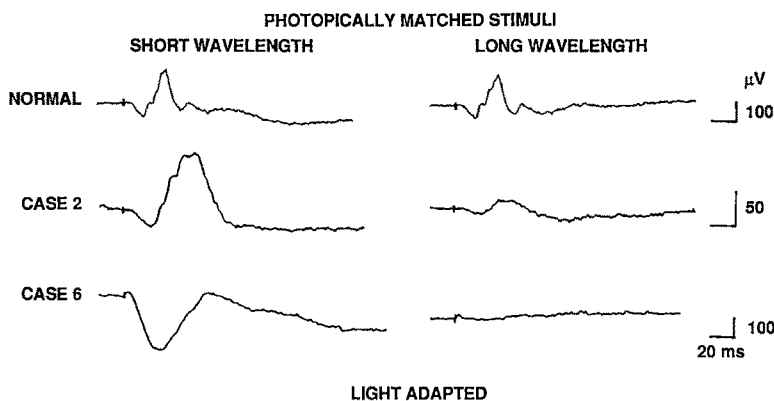
LIGHT ADAPTED

Fig. 11 (Marmor and associates). Examples of the light-adapted electroretinogram response to photopically balanced stimuli. Our patients showed a severe mismatch, with sensitivity biased markedly toward the short-wavelength stimulus. This finding is a critical diagnostic criterion for the syndrome.

the basis of symptoms, pigmentary changes, vascular narrowing, visual field loss, and loss of the electroretinogram under all conditions.

Our patients appear symptomatically similar to patients with congenital stationary night blindness, because they have poor night vision, mild to moderate loss of visual acuity, and they lack severe peripheral vision abnormalities. However, patients with congenital stationary night blindness do not have pigmentary degeneration in the arcade region or cystoid maculopathy, the scotopic electroretinogram shows a small or absent b-wave, and the cone electroretinogram is only mildly abnormal. Krill and Martin[15] described a few patients with congenital stationary night blindness and prolonged cone electroretinograms, which might represent unrecognized examples of this new syndrome (other clinical data are not available to allow a decision). The patients described by Keunen, Van Meel, and Van Norren,[5] which were shown to lack rhodopsin, also may represent examples of this disorder.

Our study does not allow a firm conclusion as to whether these patients have a stationary night blinding disorder with variable degrees (or evolution) of maculopathy or a slowly progressive dystrophy in which they are at some risk to lose peripheral visual field as well as central vision. The advanced degenerative changes in the arcade region and ring scotoma in our oldest patient (Case 8) suggest that this disorder may be progressive. There was considerable variability in expression, however, and there was no direct relationship of electroretinogram and visual field loss to age in our patients. Some of the older patients had large electroretinograms and normal visual fields, whereas younger ones had reduced-amplitude signals and scotomas. Even patients with low amplitudes may have the potential to generate

large signals, such as in Case 6. The patients who have been followed up for more than four years showed variable degrees of visual acuity loss, but little or no change in the electroretinogram and little change in the area covered by retinal degenerative changes (although the pigmentation sometimes became more prominent).

Gouras and associates[4] described patients with electroretinogram characteristics similar to our patients. Their spectral electroretinogram recordings showed that the slow photopic responses were unusually sensitive to short-wavelength light, which led them to speculate that the response may be rod-mediated, although the mechanism by which rods could be insensitive to dim illumination yet fail to saturate under photopic conditions was unclear. One of us (M.F.M.) described previously[1] the extraordinarily large rodlike photopic electroretinograms in Case 1 and speculated that insensitive but nonsaturable rods might be involved, although the scotopic b-wave failed to decrease normally in implicit time with increasing stimulus intensity. Fishman and Peachey[6] described one patient with scotopic-photopic homology and lower-amplitude electroretinogram signals and stated once again that the photopic signals were rod-mediated.

The earlier descriptions all concluded that the large slow photopic responses represented signals from the rods. However, spectral sensitivity studies on three of our patients (Cases 1, 2, and 8) disclosed that they had no measurable rhodopsin and the large photopic electroretinogram responses were derived from short wavelength-sensitive cells (420 to 460 nm) that had the spectral properties of the S cones.[7] S cone sensitivity cannot be confirmed directly by conventional electroretinogram procedures, but the finding of large slow light-adapted respons-

es that are more sensitive to blue than red light is virtually pathognomonic.

The electroretinogram waveforms of our patients resemble the S cone responses that have been recorded with specialized techniques.[15] For example, S cone responses have a long implicit time, are insensitive to dim stimuli, persist over a photopic background, fail to saturate, maintain a constant implicit time with increasing stimulus intensity, and, of course, react unequally to photopically balanced stimuli.[16] Thus, we call this newly recognized disorder the enhanced S cone syndrome. The presence of an enhanced S cone response does not by itself indicate a loss of either midspectral cones or rods, or prove the cellular origin of the electroretinogram signals. Although the rod system is extremely insensitive in these patients, we do not know whether they lack rhodopsin in structurally normal rods, have rods that contain a short wavelength–sensitive photopigment instead of rhodopsin, have few rods with an excess of structural S cones, or derive some of their apparent S cone hypersensitivity from alterations of postreceptoral circuitry.

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Cellular Immune Responses of Patients With Uveitis to Retinal Antigens and Their Fragments

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Of two patient populations totaling 82 patients, one in the United States and the other in Japan, we studied the cellular immune responses against S-antigen and interphotoreceptor retinoid binding protein as well as to fragments of each antigen. Behçet's disease, birdshot retinochoroidopathy, pars planitis, ocular sarcoid, sympathetic ophthalmia, and the Vogt-Koyanagi-Harada syndrome were diagnosed in these patients. The response profile of both antigens paralleled each other. This profile was more commonly seen in patients suffering from diseases affecting the retina. Responders reacting to both antigens or to several fragments of an antigen were present. This pattern of response was seen in 26 of the patients tested. Patients with uveitis appeared able to recognize several autoantigens. This might be a consequence of the breakdown of the blood-retinal barrier and may help perpetuate the inflammatory process. Several patients were capable of responding to more than one epitope of the same antigen, which indicates that there are major differences between the experimental model and human autoimmune diseases in the response to autoantigens. Both of these findings may to help develop new immunotherapeutic strategies in the treatment of uveitis.

Intraocular inflammatory disease (uveitis) is the cause of about 10% of severe visual loss in the United States.[1] The understanding of underlying mechanisms has been increased by the development of an experimental uveitis model in animals, induced either by the retinal S-antigen or by the interphotoreceptor retinoid binding protein.[2-5] Nussenblatt and associates,[6,7] Doekes and associates,[8] and Froebel and associates[9] have described patients with uveitis who have cell-mediated responses to these antigens. Several fragments of both antigens have been identified as being uveitogenic in animals.[10-12] Observations from experimental autoimmune uveitis as well as other models of autoimmune disease have clearly demonstrated that the immune systems of different species respond to different epitopes (that is, fragments) of a given molecule. Cell-mediated and humoral responses are invariably directed against different parts of the molecule.

We examined the cell-mediated responses of patients with uveitis to both of these uveitogenic molecules, as well as to representative fragments that have been reported as being uveitogenic in both lower mammals and in subhuman primates. These responses may encourage the development of treatment strategies using these molecules and fragments.

Patients and Methods

Patients participating in this study were seen in the uveitis clinic of the National Eye Institute, Bethesda, Maryland, and at the Tokyo University Branch Hospital, Tokyo, Japan. All patients gave informed consent before participating in the study. They were part of an ongoing protocol approved by each institution's committee on human investigation. All patients had active uveitis involving the posterior segment or had a history of active disease involving the retina or choroid. The patients

tested had one of the following disorders: Behçet's disease, birdshot retinochoroidopathy, pars planitis, ocular sarcoid, sympathetic ophthalmia, or the Vogt-Koyanagi-Harada syndrome.[13] Patients with Behçet's disease met at least the minimal criteria for incomplete Behçet's set by the Behçet's Disease Research Committee of Japan[14] with all patients having ocular disease. Patients with birdshot retinochoroidopathy had cream-colored lesions in the posterior segment, macular edema, and retinal vascular changes. These patients were HLA A-29 positive as well. Patients with sympathetic ophthalmia had a history of penetrating trauma or multiple operations followed by a bilateral granulomatous uveitis. Patients with Vogt-Koyanagi-Harada syndrome were of either Japanese or American Indian heritage and had ocular and systemic changes compatible with the disorder. The patients with ocular sarcoid had bilateral granulomatous uveitis usually accompanied by either a positive gallium scan or a noncaseating granuloma on a biopsy specimen. Patients were tested irrespective of their current medical therapy (usually consisting of cyclosporine, prednisone, or both) or of their level of activity. Since the antigens tested were of retinal origin, anterior segment inflammation was not considered as part of the definition of active disease. The presence of retinal infiltrates, perivasculitis, snowbanking, or vitreous haze were accepted as evidence of activity. Additionally, cystoid macular edema confirmed by fluorescein angiography was considered a sign of active disease. All the diagnostic categories were based on clinical criteria except ocular sarcoid and birdshot retinochoroidopathy, in which confirmation by another test was required. Control subjects were selected from either nonresearch staff or from clinic patients not being seen for a uveitic condition, and in whom a retinal or choroidal disorder had been ruled out.

Antigens used in this assay included bovine interphotoreceptor retinoid binding protein purified to homogeneity, as described by Redmond and associates,[15] and bovine S-antigen purified by the method described by Dorey, Cozette, and Faure.[16] Peptides derived from interphotoreceptor retinoid binding protein were synthesized and purified by Applied Biosystems Inc., Foster City, California, using the t-BOC chemistry, on a peptide synthesizer 430A. The peptide sequences were derived from the sequence of bovine interphotoreceptor retinoid binding protein as determined and

reported by Borst and associates.[17] This consisted of sequence 1158-1180 (HVDDTDLYLTIP-TARSVGAADGS) for R-4 and of sequence 1169-1191 (PTARSVGAADGSSWEGVGVVP-DV) for R-14. Peptides derived from S-antigen were based on the bovine S-antigen sequence reported by Shinohara and associates.[18] The peptides were synthesized in accordance with the method of Donoso and associates,[19] on a benzhydrylamine resin using an automated peptide synthesizer (SAM II, Biosearch, Inc., San Rafael, California). The sequence for peptide M corresponded to positions 303 to 320 (DTNLASSTIIKEGIDKTV), and peptide N corresponded to positions 281 to 302 (VPLLANN-RERRGIALDGKIKHE) of the S-antigen.

Proliferation assays were performed in the same way in Japan and the United States, except where indicated. Mononuclear leukocytes from heparinized blood samples were separated on Isolymph gradients (Gallard-Schlesinger, Carle Place, New York) and cultured in Roswell Park Memorial Institute (RPMI) 1640 medium with HEPES (GIBCO, Grand Island, New York), supplemented with glutamine (2 mmol/l), penicillin (100 units/ml), streptomycin (100 μg/ml), and heat inactivated human AB serum. The National Eye Institute used 20% serum from a single donor in the cultures, whereas Tokyo University Branch Hospital used 10% commercial serum (lot No. 14510, Pel Freez, Brown Deer, Wisconsin).

The cells were cultured by two methods. In the first method, 2×10^5 cells/well were incubated in flat-bottom, 96-well plates for five days.[6] In the second method, which under certain circumstances is believed to increase responses by increasing cell to cell interactions, 5 $\times 10^4$ cells/well were incubated in round-bottom, 96-well plates for seven days.[20] All cultures were in a total volume of 200 μl and were set up in triplicate with or without stimulants. The antigen concentration was either 4, 20, 50, or 100 μg/ml. The cultures were incubated for the specified time at 37 C with 100% humidity and 5% carbon dioxide in air, pulsed for 16 hours with ^{3}H-thymidine (^{3}H-TdR, New England Nuclear, Boston, Massachusetts; 2 Ci/mmol, 0.5 μCi per 10 μl/well) and harvested on glass fiber filters using a MASH II harvester. After drying, the filter pads were placed in vials with 3 ml of toluene-based fluor and counted in a Beckman L3801 liquid scintillation counter. Several peptides were tested simultaneously; however, not all peptides could be tested on each patient. Cells from a control subject were

usually tested simultaneously with cells from one or more patients.

The mean of the triplicate cultures in counts per minute was calculated for each set of replicate cultures. A stimulation index was derived by dividing the mean for each of the antigen stimulated cultures by the mean for the control cultures in which no antigen was added. For each testing center and for each antigen, a mean stimulation index ± standard deviation was calculated for the control subjects. A significant response in a patient was considered to be present when the patient's stimulation index for a given peptide or determinant was above the mean for the controls by two S.D. ·

The stimulation indices for each antigen tested were also compared by disease category to the control subjects to determine if any statistically significant difference was present. Significance was assessed by a standard nonpaired Student's t-test. Patients were also assessed by their clinical activity. Testing for statistical significance was done using chi-square. Results are given as the mean stimulation index ± standard error.

Results

A total of 30 control subjects and 82 patients were tested; 47 patients were from the United States and 35 patients were from Japan. The average age of the patients in both groups was comparable; 41 years of age (range, 10 to 70) for the American patients and 43 years of age (range, 20 to 70) for the Japanese. The duration of follow-up was also similar in the two groups: 44 months in the United States (range, six to 108) and 57 months in Japan (range, two to 247). On average, uveitis had been diagnosed in the patients for 63 months (range, two to 247). All of the patients examined in Japan were of Japanese descent, whereas in the American group, 41 patients were white, five were black, and one patient was Oriental. The number of patients with clinically active disease varied among the various categories (Table 1) and between countries. Overall, half of the patients tested had active ocular disease. The largest discrepancy was found among patients with sarcoid, in which a greater number of the Japanese patients had active disease. Of all the groups, the patients with birdshot retinochoroidopathy had the lowest incidence of activity, and none were tested in Japan, where the disease is extremely rare. The proportion of patients with active disease was highest among those suffering from Behçet's disease.

The various disease entities responded differently to the uveitogenic antigens (Table 2). A similar response profile, however, was found for S-antigen and interphotoreceptor retinoid binding protein. Patients with diseases involv-

TABLE 1
CHARACTERISTICS OF AMERICAN AND JAPANESE PATIENTS

CLINICAL ENTITY	TESTING CENTER	MEAN AGE (YRS)*	DURATION OF DISEASE (MOS)*	NO. OF PATIENTS	MALE/ FEMALE	CLINICAL ACTIVITY ACTIVE/INACTIVE	THERAPY CYCLOSPORINE	PREDNISONE	CYTOTOXICS
Behçet's disease	U.S.	34 (28-42)	50 (10-96)	8	5/3	5/3	4	8	—
	Japan	38 (24-60)	54 (12-126)	16	16/0	11/5	8†	4	2
Vogt-Koyanagi-	U.S.	34 (24-60)	33 (6-60)	9	1/8	2/7	2	4	—
Harada syndrome	Japan	47 (29-65)	93 (4-247)	10	5/5	0/10	1	7	1
Ocular sarcoid	U.S.	50 (34-61)	32 (7-72)	9	8/1	5/4	2	4	—
	Japan	45 (20-70)	43 (2-180)	9	3/6	6/3	0	5	—
Pars planitis	U.S.	31 (16-49)	45 (24-60)	6	2/4	5/1	2	3	—
Birdshot retino- choroidopathy	U.S.	56 (46-66)	67 (24-108)	9	5/4	1/8	2	2	—
Sympathetic ophthalmia	U.S.	52 (10-70)	36 (6-72)	6	2/4	4/2	1	5	—
Normal	U.S.	35 (26-50)	—	20	10/10	—	—	—	—
	Japan	37 (14-67)	—	10	6/4	—	—	—	—

* Average. The range is given in parentheses.
† Nine patients with Behçet's disease also received colchicine.

TABLE 2
RESPONSES TO PEPTIDE DETERMINANTS OF INTERPHOTORECEPTOR RETINOID BINDING PROTEIN AND S-ANTIGEN UNDER OPTIMAL CULTURE CONDITIONS*

ANTIGEN TESTED	BEHÇET'S DISEASE		VOGT-KOYANAGI-HARADA SYNDROME		OCULAR SARCOID		BIRDSHOT RETINO-CHOROIDOPATHY	PARS PLANITIS	SYMPATHETIC OPHTHALMIA
	U.S.	JAPAN	U.S.	JAPAN	U.S.	JAPAN	U.S.	U.S.	U.S.
Interphotoreceptor retinoid binding protein	3/8	6/16	1/9	1/10 4/10†	0/9	0/9 3/9†	1/9	2/6	2/6
R-4	4/8	—	2/9‡	—	1/9	—	5/9‡	1/6‡	2/6‡
R-14	2/8	2/16	2/9‡	3/10	2/9‡§	2/9	3/9‡	1/5‡	2/5
S-antigen	3/8	3/16§	4/9‡	2/10§	1/9§	0/9	3/9	1/6	1/6
M peptide	6/8	2/16§	4/9	1/10§	3/9	3/9§	3/9	1/6	0/6
N peptide	3/4‡	6/16§	1/4	5/10§	0/4	7/9§	4/9	0/6	1/5‡

* The numerator refers to the number of positive responders. The denominator refers to the total number of patients tested. In most cases, five-day cultures with 20 μg/ml of antigen in each well were found to be optimal except where indicated.

† Cells were cultured with 4 μg/ml for seven days.

‡ Antigen concentration was 100 μg/ml.

§ Cells were cultured for seven days with 20 μg/ml of antigen.

ing the retina were more likely to have a significant proliferative response. In American patients, the mean proliferative responses to the S-antigen (20 μg/ml) were significant for Behçet's disease, 2.8 ± 1.0 (P = .05) and birdshot retinochoroidopathy, 2.7 ± 0.7 (P = .02) whereas the control was 1.3 ± 0.2. For the interphotoreceptor retinoid binding protein (20 μg/ml), the proliferative responses were lower, with a significant difference in Behçet's disease, 1.5 ± 0.4 (P = .04), birdshot retinochoroidopathy, 1.4 ± 0.3 (P = .04), and pars planitis, 1.4 ± 0.02 (P = .04) as compared to the control, 0.9 ± 0.1. A similar pattern of response was found in the Japanese patients, with the highest number of responders found in Behçet's disease. The patients with ocular sarcoid gave few positive responders. Their responses to phytohemagglutinin and purified protein derivative, however, were strong, which indicates that the lack of response is not caused by a generalized state of unresponsiveness, but probably reflects an inability to recognize bovine S-antigen or bovine interphotoreceptor retinoid binding protein. Culturing the cells for seven days in round-bottom wells increased the number of significant responses in some groups, but not in all. There was an increase in sensitivity mainly for patients with the Vogt-Koyanagi-Harada syndrome where there was an increase in the number of significant responders to the S-

antigen and the interphotoreceptor retinoid binding protein. The mean response to the S-antigen for lymphocytes from patients with Vogt-Koyanagi-Harada syndrome in the United States was 2.8 ± 1.4, as compared to control subjects (1.8 ± 0.1), which was a statistically significant difference (P = .03).

In addition to testing in vitro responses to the interphotoreceptor retinoid binding protein and the S-antigen, the responses to peptide fragments of each of these antigens were determined (Table 2). There was a correlation between the intensity of the proliferative response to the interphotoreceptor retinoid binding protein or the S-antigen and the existence of a significant proliferative response to one or more of the peptide fragments of that antigen. In five-day cultures, if considering only statistically significant responders to S-antigen, seven of nine American patients had a significant response to one or both peptide fragments tested. In seven-day cultures, three of five Japanese patients responsive to S-antigen had a response to either M peptide or N peptide, or to both. In six of the nine American patients who responded to the interphotoreceptor retinoid binding protein, there was a response to either R-4 or R-14, or to both. No such correlation was seen in the Japanese responders to interphotoreceptor retinoid binding protein.

Several patients' lymphocytes had a proliferative response to a peptide fragment, but did not recognize the parent antigen. In 12 of 22 American patients (54%) responding to one or the other S-antigen fragment at 20 or 100 μg/ml in five-day cultures, there was no cross reaction with the whole molecule. Under similar conditions, the responses to interphotoreceptor retinoid binding protein fragments gave no cross reaction in 16 of 20 (84%) American patients. The Japanese responders to S-antigen fragments recognized S-antigen in only six of 19 cases (cells cultured for seven days).

Patients with Behçet's disease showed a response to fragments of both antigens but the responses were strongest for fragments of S-antigen. At 20 μg/ml, M peptide gave the highest response with a mean stimulation index of 5.3 ± 1.0 for patients and 1.3 ± 0.2 for control subjects (P = .0001). The response to N peptide was also significant with patients having a mean stimulation index three times higher than control subjects. Patients with birdshot retinochoroidopathy had similar responses to both sets of fragments. The mean stimulation indices in patients were twice those of control subjects for both sets of fragments.

Several patients demonstrated an ability to give simultaneously a significant proliferative response to at least one determinant of each antigen, but not necessarily to the whole antigen. A total of 32 patients out of the 82 patients tested (39%) were found to give such responses, 18 among the American patients and 14 among the Japanese patients. They were found in all disease categories but were more frequently found among the patients with Behçet's disease or birdshot retinochoroidopathy. A similar distribution of patients was found in the two countries. Of the American patients 11 had active disease at the time they gave a response to both antigens as compared to six of 18 nonresponders (P = .02). There is little difference, however, with the number of patients with active disease (seven of 11 patients) responding to only one antigen (P = .05). A correlation between active disease and a significant lymphoproliferative response was not found among the Japanese patients.

In comparing S-antigen to interphotoreceptor retinoid binding protein, it appears that S-antigen is more frequently correlated with active disease (P = .003). As is shown in Table 3, however, the profile in each disease entity is similar for the two antigens. An attempt was

TABLE 3
RELATIONSHIP BETWEEN CLINICAL ACTIVITY AND THE PRESENCE OF A SIGNIFICANT LYMPHOCYTE RESPONSE TO INTERPHOTORECEPTOR RETINOID BINDING PROTEIN AND S-ANTIGEN*

CLINICAL ENTITY	TESTING CENTER	INTER- PHOTO- RECEPTOR RETINOID BINDING PROTEIN	S-ANTIGEN
Behçet's disease	U.S.	2/7	3/7
	Japan	6/9	3/4
Vogt-Koyanagi-Harada syndrome	U.S.	0/2	1/2
	Japan	0/5	0/2
Ocular sarcoid	U.S.	1/5	1/5
	Japan	2/3	0/0
Pars planitis	U.S.	2/5	2/5
Birdshot retinochoroidopathy	U.S.	0/1	0/1
Sympathetic ophthalmia	U.S.	1/4	2/4

* Numerator refers to those patients with active disease. The denominator refers to all patients with a significant proliferative response to the antigen at 20 μg/ml or 100 μg/ml. The data include all responders with a stimulation index above 2.0 in both five- and seven-day cultures.

made to correlate proliferative responses with therapy, but no correlation was possible. Patients with active disease were more likely to be treated with cyclosporine or prednisone.

Discussion

Our aim in this study was twofold. First, we wanted to determine the response profile of interphotoreceptor retinoid binding protein in patients with uveitis and to compare it to that of S-antigen. Secondly, we wanted to determine whether patients were able to respond to fragments of these antigens, which have been shown to be uveitopathogenic in animals. Since the cellular immune response centers around different epitopes in different animal species, we did not know if patients would be able to react to any of these fragments in cellular proliferation assays.

Several previous studies demonstrated that cellular proliferative responses to S-antigen

were present in inflammatory conditions affecting the posterior pole, and in particular the retina of patients with uveitis.[6,7] Table 2 suggests that the response profile for interphotoreceptor retinoid binding protein is nearly identical to that of S-antigen. Patients with Behçet's disease gave the highest number of positive responders. This was true whether the data were analyzed in terms of the number of patients with a stimulation index substantially above that of control subjects, as in Table 2, or using the Student's t-test, which compares each group as a whole. Using the Student's t-test, a significant response to interphotoreceptor retinoid binding protein is also found in patients with birdshot retinochoroidopathy, even though Table 2 does not show this result. The discrepancy develops from a few control subjects who were able to give a strong proliferative response to the antigens tested, which caused a substantial increase in the value of the standard deviation.

Interphotoreceptor retinoid binding protein does not appear to be as predictive of active disease as is S-antigen (Table 3). There are, however, more patients responding to interphotoreceptor retinoid binding protein than to S-antigen. In the Japanese population, the number of patients with active disease who respond to interphotoreceptor retinoid binding protein is greater. A much larger number of patients would be required to determine the exact relationship to disease activity. Patients who show an ability to proliferate concurrently to both antigens have a slight increase in their probability of having active disease, but the difference did not reach statistical significance. In relation to the mechanism of disease induction and its propagation, it is the existence of a response in culture and its greater prevalence in patients with active disease that is significant. In a given patient, an in vitro proliferative response indicates that lymphocytes sensitized to the antigen tested are circulating in the peripheral blood. In the animal models, sensitized lymphocytes capable of an in vitro proliferative response were one of the necessary conditions for the induction of autoimmune disease.[21,22] It is likely, however, that the induction of uveitis is caused by multiple factors. Therefore, it is not surprising to find some control subjects whose lymphocytes demonstrate an in vitro response to these antigens. Sensitization to these antigens might occur through a variety of means such as minor trauma or mimicry with other peptides.[23] We believe

that the difference between a patient and a control subject lies in the inability of control subjects to initiate an inflammatory response or to maintain it once initiated. This could occur because all of the mechanistic criteria have not been met or because suppressor mechanisms are strong enough to shut down the response.[24]

The ability of some patients to respond to both retinal antigens in culture is a unique finding, which may help to elucidate certain aspects of the mechanisms involved in chronic uveitis. We believe that a patient is initially sensitized to probably only one antigen; however, after the breakdown of the blood-retinal barrier,[25] the immune system becomes exposed to several new sequestered antigens. These autoantigens are likely processed by circulating or resident antigen presenting cells.[26,27] Partial digestion of the antigen will generate fragments that are then able to associate with appropriate class II antigens.[28] In the presence of these antigens a complex is formed, which when expressed on the cell surface is able to interact and activate T lymphocytes. These activated, proliferating T lymphocytes can potentiate an acute inflammatory episode and possibly help perpetuate the inflammatory episode.

Patients who responded to S-antigen or interphotoreceptor retinoid binding protein were able to recognize one or both fragments tested, but none of the responses to the fragments were of a similar magnitude to that of the parent antigen. This lesser response suggests that these fragments do not appear to be the primary mediators of the cell-mediated immune response in humans. Hence, we conclude that they are not immunodominant sites.[29,30] Some patients demonstrated an ability to generate an in vitro response to both fragments of a given antigen. This capacity to recognize more than one epitope of S-antigen and interphotoreceptor retinoid binding protein was not found in the animal model. In the Lewis rat, immunization with interphotoreceptor retinoid binding protein generates a strong proliferative in vitro response to peptide R-14,[12] whereas R-4, which we also tested, is a nondominant fragment and is not recognized by animals immunized with the whole protein.[31] In the case of S-antigen, only one immunodominant site has been reported.[32] It is likely that this disparity reflects a fundamental difference between the experimental model and naturally occurring autoimmune diseases. Future studies are needed to elucidate the importance of the various epitopes of S-antigen and interphotoreceptor

retinoid binding protein. Although most responders to S-antigen and interphotoreceptor retinoid binding protein were able to respond to one or both fragments of these antigens, most of the responders to the fragments were not able to recognize the parent antigen.

This study shows that interphotoreceptor retinoid binding protein has a response profile that is virtually identical to that of S-antigen. Several patients were able to mount a response to both antigens in culture. Several patients also showed the ability to respond to more than one epitope of a given antigen. Both phenomena indicate that human disease is much more complex than suggested by the current autoimmune models of disease. Several autoantigens appear to be implicated in chronic uveitis in humans, and the interactions between each of these antigens is unknown. The extent of the plurispecificity of response to autoantigens also remains to be determined. It may be a generalized characteristic of human class II antigens, and it is also possible that patients possess an enhanced ability to interact with several different fragments as compared to normal individuals. Further studies on cell lines, and by using multiple fragments of the antigens, may help answer these questions.

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OPHTHALMIC MINIATURE

What's wrong with my eyes? My field of vision is narrowing from top to bottom. The world looks as if it were seen through the slit of a gun turret. But of course! My eyes are swelling with hives! It could only come from the delicious gin fizzes prepared for me by Lola, my lovely cellist.

Walker Percy, *Love in the Ruins*
New York, Ivy Books, 1971, p. 18

Distinctive Cataract in the Stickler Syndrome

Christopher M. Seery, M.D., Ronald C. Pruett, M.D., Ruth M. Liberfarb, M.D.,
and Ben Z. Cohen, M.D.

We determined the clinical characteristics of cataract in 133 patients with the Stickler syndrome. Cataracts of various types or aphakia were found in 115 of 231 eyes (49.8%) studied. The most frequent and distinctive lesions, described as wedge and fleck cataracts, accounted for 40 of the 93 cataracts (43.0%) observed. These distinctive opacities may serve as a clinical marker for the Stickler syndrome and facilitate early diagnosis.

STICKLER SYNDROME is an autosomal dominant, inherited disorder with several ocular and systemic manifestations including myopia, strabismus, glaucoma, vitreoretinal degenerative changes with retinal detachment, cataract, flat facies, micrognathia, palatal abnormalities, hearing impairment, early onset arthropathy, mild epiphyseal dysplasia, and mitral valve prolapse. Various types of lens opacities have been observed in studies of limited numbers of patients.[1-5] This investigation was conducted to determine more precisely the prevalence and characteristics of cataract in patients with Stickler syndrome.

Patients and Methods

Computer-selected records of 133 patients with Stickler syndrome were reviewed. All patients had a genetic and systemic examination by one of us (R.M.L.). The diagnosis was based on the presence of ocular, orofacial, cardiac, and skeletal signs of the disorder.[6-8] All pro-

bands without family members available for examination had a family history consistent with an autosomal dominant hereditary pattern. Most of the patients were white, three were Hispanic, and two were Asian. Various nationalities were represented among the whites, including French, German, Italian, Irish, and Lebanese. There were 71 (53.3%) male patients and 62 (46.7%) female patients whose ages ranged from 3 to 76 years (mean, 30.7 years). All but ten patients were in 40 families, which contained two to six affected members.

A complete ocular examination, including biomicroscopy of the anterior segment, had been done on all 133 patients. Two eyes had been enucleated, and in 33 eyes the description of lens findings was insufficient for evaluation. Among the 231 remaining eyes, 22 were aphakic at the time of their initial examination. Detailed notations of lenticular status in 209 eyes were analyzed and categorized according to appearance and location.

Results

Cataract or aphakia was found in 115 of 231 eyes (49.8%). The prevalence of lens abnormalities according to age is shown in Table 1. Cataract occurred in children less than 10 years of age but became more frequent in older patients. Cataract or aphakia was present at the time of first examination in 40 of 129 eyes (31.0%) of patients who were 20 years of age or less, and in 39 of 61 eyes (63.9%) of patients who were 21 to 40 years of age. Among 41 eyes of patients who were 41 to 76 years of age, the lens was clear in only five (12.2%).

The types of lens opacities encountered in each age decade are shown in Table 2. Isolated posterior subcapsular cataract was seen in younger patients; after age 30 it was seen more often in combination with nuclear sclerosis. Nuclear sclerosis without additional lens opacities was found only in patients who were 41 years of age or older. In eight eyes, the lens

TABLE 1

AGE DISTRIBUTION OF LENS FINDINGS IN THE STICKLER SYNDROME

LENS FINDING	AGE (YRS)						TOTAL NO.
	3–10	11–20	21–30	31–40	41–50	51–76	
Total No. of eyes	24	116	28	46	26	26	266
Lens undescribed	—	10	4	9	6	4	33
Enucleated	—	1	—	—	—	1	2
No. of eyes studied	24	105	24	37	20	21	231
Aphakic	1	5	1	5	4	6	22
Cataract	6	28	13	20	12	14	93
Lens clear	17	72	10	12	4	1	116

TABLE 2

CATARACT APPEARANCE IN THE STICKLER SYNDROME

CATARACT APPEARANCE	AGE (YRS)						TOTAL NO.
	3–10	11–20	21–30	31–40	41–50	51–76	
Isolated nuclear sclerosis	—	—	—	—	2	7	9
Isolated posterior subcapsular	4	8	3	4	1	1	21
Nuclear sclerosis and posterior subcapsular	—	—	1	6	3	5	15
Dense	2	2	1	2	—	1	8
Distinctive*	—	18	8	8	6	—	40

*Distinctive indicates distinctive lesions classified as wedge or fleck.

opacity was too dense to classify anatomically. The most frequent type of cataract observed consisted of discrete, dense, white or gray, peripheral, cortical opacities. These were called distinctive.

·Distinctive cataracts were found in 40 eyes: 19.1% of the 209 phakic eyes studied and 43.0% of the 93 cataractous eyes studied. Opacities varied in size, shape, number, and arrangement. They occupied a similar flat lamella within the cortex with adjacent lens regions appearing clear. Some were oriented radially,

with a broader peripheral margin forming an approximate wedge shape (Fig. 1). These lesions varied somewhat in size, averaging 2.5 × 2.5 mm. Others consisted of one to as many as five punctate flecks (approximately 0.5 × 1.0 mm) arranged radially (Fig. 2). Such flecks were limited to a specific region of the cortex and a specific lamellar depth. The silhouettes of wedge and fleck lesions produced by retroillu-
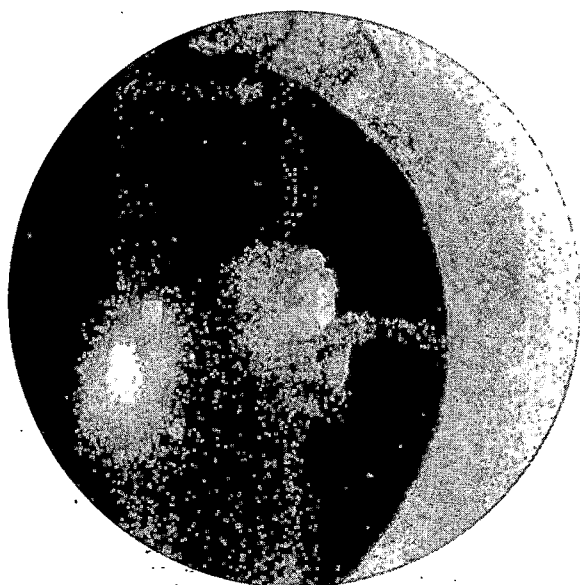
Fig. 1 (Seery and associates). Slit-lamp photograph demonstrating wedge cataract (arrow) observed in the left eye of a 33-year-old patient with the Stickler syndrome.
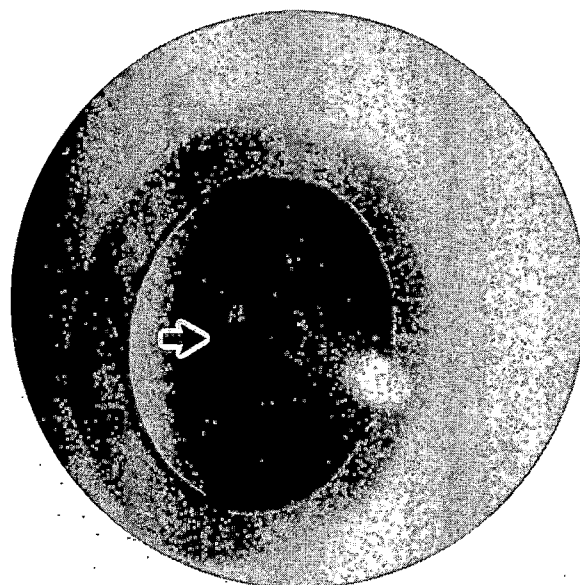
Fig. 2 (Seery and associates). Slit-lamp photograph demonstrating fleck cataract (arrow) observed in the right eye of a 25-year-old patient with the Stickler syndrome.

mination appeared similar. Direct illumination, however, disclosed a fibrillar, sharp border to wedge lesions, whereas fleck lesions had a softer, rounded edge. No distinctive opacities were found in the axial zone of the anterior or posterior cortex.

The 40 distinctive cataracts were noted in 25 patients, 14 (56.0%) male and 11 (44.0%) female. Of these cataracts, 31 (77.5%) showed a wedge defect; nine (22.5%) showed flecks. Of the patients, 15 (60.0%) were bilaterally affected. Bilateral opacities were usually of the same shape; only one patient had a wedge defect in one eye and a fleck defect in the other. Among the ten unilateral cases, nine lenses of fellow eyes were clear and one was densely opaque.

Wedge and fleck lesions were further classified as to their anterior or posterior location (Table 3). Of 31 wedge lesions, 21 (67.8%) were located anteriorly. Fleck lesions were distributed in both the anterior and posterior cortex of the same lens in six (66.7%) of nine lenses with such opacification. Both wedge and fleck lesions tended to be bilateral (Table 4). Of the 40 cataracts, 22 (71.0%) of 31 wedge lesions and six (66.7%) of nine fleck lesions were bilateral. When the wedge opacity appeared symmetrically (45.0%), the opacities were of similar size, shape, and quadrantic location (Fig. 3). In no case were wedge and fleck opacities seen in a single lens.

At least two members of each of five families had distinctive cataracts. In three families both types of opacities were observed; wedges appeared in one member and fleck lesions in others. In eyes without the common lenticular opacities of aging and without retinal disease,

TABLE 3

SPATIAL DISTRIBUTION OF DISTINCTIVE CATARACTS IN THE STICKLER SYNDROME

TYPE OF LESION	AGE (YRS)						TOTAL NO.
	3–10	11–20	21–30	31–40	41–50	51–76	
Wedge							
Anterior	—	13	2	4	2	—	21
Posterior	—	3	2	2	3	—	10
Fleck							
Anterior	—	1	2	—	—	—	3
Posterior	—	—	—	—	—	—	0
Anterior and posterior	—	1	2	2	1	—	6

TABLE 4

LATERALITY OF DISTINCTIVE CATARACTS IN THE STICKLER SYNDROME

TYPE OF LESION	AGE (YRS)						TOTAL NO.
	3–10	11–20	21–30	31–40	41–50	51–76	
Wedge							
Bilateral	—	10	4	4	4	—	22
Unilateral	—	6	—	2	1	—	9
Fleck							
Bilateral	—	—	4	2	—	—	6
Unilateral	—	2	—	—	1	—	3

wedge and fleck opacities did not reduce visual acuity.

Rhegmatogenous retinal detachment was observed in 96 of the 231 eyes (41.6%) studied (Table 5). Among phakic eyes, 33 of 116 (28.4%) with a clear lens and 15 of 40 (37.5%) with a distinctive cataract were found to have retinal detachment (P = .285). In comparison, 37 of 53 eyes (69.8%) with lens opacities other than the distinctive type had a retinal detachment (P = .0004). In the group of 22 patients with aphakia, 11 (50.0%) had retinal detachment. No patient had previous retinal reattachment surgery.

Discussion

Cataract is common in the Stickler syndrome. Of the 209 eyes with documented lens findings in this series, 93 (44.5%) showed some type of opacity. An additional 22 eyes were already aphakic when first examined. Even assuming that detailed lens descriptions were not found for 33 eyes because the lenses were clear, cataract or aphakia was noted in 115 of the 264 eyes (43.6%) observed. Cataract or aphakia increased with age from 29.2% of 24 eyes of patients who were 10 years of age or younger to 87.0% of 42 eyes of patients who were 41 to 76 years of age. Opacities were more common bilaterally than unilaterally and had no sex predilection. Nuclear sclerosis and posterior subcapsular opacification, similar to that appearing in a more senescent population, were noteworthy because of their premature appearance. Knobloch[9] reviewed earlier studies and concluded that cataract occurred frequently in the Stickler syndrome but varied widely among
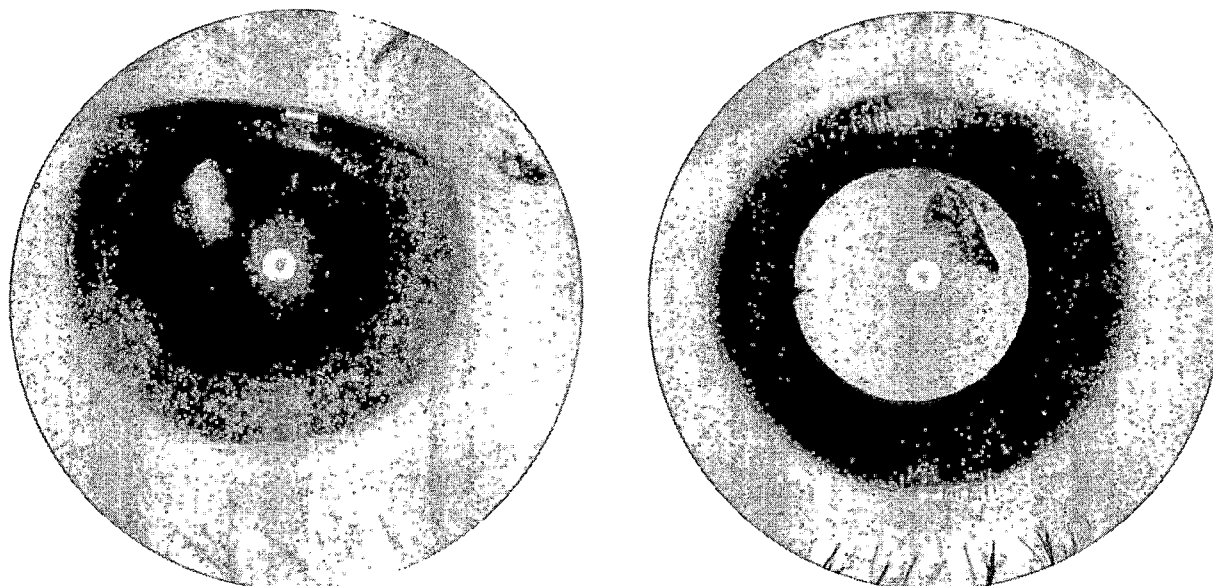
Fig. 3 (Seery and associates). Slit-lamp photographs demonstrating symmetry of upper temporal wedge cataracts in a 17-year-old patient with the Stickler syndrome. Left, Right eye (direct illumination). Right, Left eye (retroillumination).

affected families. O'Donnell, Sirkins, and Hall[10] found cataract in 34% of 33 patients. Jansen[11] discovered cataract in all patients over the age of 10 in the two families studied. Liberfarb, Hirose, and Holmes[6] reported the prevalence of cataract as 47% in 70 members of 22 families. In that study, the prevalence of cataract increased from 20% in patients less than 10 years of age to 83% in those over 50 years of age.

The variability in phenotypes previously reported for Stickler syndrome may be the result of at least two factors. First, a genetic heterogeneity has been demonstrated among affected families. Francomano and associates[12] reported that a mutation in the type II collagen genome may be the causative factor in the Stickler syndrome. They found no recombinants with a total LOD score of 3.59 at $\Theta = 0$ for linkage of the Stickler syndrome and COL2A1. Exclusion of linkage to COL2A1 has been shown in three other families.[13,14]

Second, some confusion has existed regarding the differentiation of Stickler syndrome from other hereditary vitreoretinopathies. After Wagner[15] described a Swiss family with an autosomal dominant inherited vitreoretinopathy in 1938, a number of articles reported similar findings in association with increased prevalence of retinal detachment, a feature not reported in Wagner's study. Alexander and Shea[16] suggested the eponym "Wagner's dis-

ease" be applied to the disorders. Subsequently, extraocular manifestations were described including unusual facial appearance with midfacial hypoplasia and occasional palatal abnormalities, hearing loss, and musculoskeletal abnormalities.[17-20]

In 1965 and 1967, Stickler and associates[21] and Stickler and Pugh[22] described the expression of the Stickler syndrome in multiple members of several generations of a family. The predominant features of this disorder include severe myopia, cataract, retinal detachment, cleft palate, a premature osteoarthropathy, and high-tone sensorineural hearing loss.[2,23] Opitz,

TABLE 5

PREVALENCE OF RETINAL DETACHMENT ACCORDING TO AGE AND LENS STATUS IN PATIENTS WITH STICKLER SYNDROME

	AGE (YRS)					
	3–10	11–20	21–30	31–40	41–50	51–76
LENS STATUS	(NO. OF EYES WITH RETINAL DETACHMENT/ TOTAL NO. OF EYES)					
Clear	3/17	21/72	7/10	0/12	2/4	0/1
Cataract*	5/6	8/10	4/5	9/12	3/6	8/14
Distinctive cataract	—	9/18	1/8	1/8	4/6	—
Aphakic	1/1	2/5	1/1	1/5	4/4	2/6

*Eyes with cataract other than distinctive type.

France, and Hermann[24] first suggested that cases representing the Stickler syndrome had been reported under different designations. Members of a number of families reported as having Wagner disease[19] were reexamined by one of us (R.M.L.) and found to have extraocular features consistent with the Stickler syndrome.[6,7] The eponym Wagner-Stickler syndrome was proposed but not widely accepted.

Francomano and associates[13] tested the hypothesis that the Stickler syndrome and the Wagner syndrome were allelic by performing linkage analysis using COL2A1 probes in the Swiss family originally studied by Wagner. Recombinant events between the Wagner mutation and polymorphic markers associated with COL2A1 excluded mutations in type II collagen as the cause of the hereditary condition described by Wagner. Additionally, Maumenee, Stoll, and Mets[25] examined five members of the family originally studied by Wagner. Although the vitreous and retinal degenerative changes noted in these patients appeared similar to that described in Stickler syndrome, none had retinal detachment or the extraocular features of this entity.

Retinal detachment was a frequent occurrence among our patients, with 96 of 231 eyes (41.6%) affected. This high prevalence most likely reflects the referral nature of our practice. Compared to eyes with a clear lens, those eyes with a distinctive cataract had no statistically significant increase in retinal detachment (P = .285). However, those eyes with cataract other than wedge or fleck lesions were more likely (P = .0004) to have retinal detachment. Since posterior subcapsular cataract was most common in this latter group, it is possible that chronic uveitis secondary to retinal detachment played some role in their occurrence.

The large cohort of patients in our series clearly had the Stickler syndrome based on a thorough ocular and systemic examination. Most striking was the occurrence of distinctive wedge and fleck opacities. These were the most frequently encountered opacities and accounted for 40 of the 93 cataracts (43.0%) found. Although observed previously in the Stickler syndrome,[10,18] these opacities had not been completely characterized. Such wedge and fleck cataracts may represent a clinical marker of the Stickler syndrome. Their occurrence in young children suggests also that they may be congenital and might serve as an aid to early diagnosis. Recognition of the Stickler syndrome is important for prompt diagnosis and

treatment of associated complications such as glaucoma and retinal detachment, for detection of the syndrome in other family members, and for referral to examine the medical and orthopedic status of affected patients.

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OPHTHALMIC MINIATURE

I looked at my father. Jacob was sitting between us and had a short yellow pencil poised against the scorecard. I looked straight at my father and said, "A double, just a double." For a second I thought I heard his heart crack, but it was the crack of the bat. Everyone in the stadium jumped to his feet except my father and me. We sat in a roaring, headless forest of bodies, our eyes locked. His smile was gone and his eyes were vacant, as if someone had slid a small knife between his shoulder blades. Then his expression softened, and I looked away.

Richard Zabel, *The Swan*
Atlantic Monthly, May 1990, p. 98

The Results of Penetrating Keratoplasty for Pellucid Marginal Corneal Degeneration

Gary A. Varley, M.D., Marian S. Macsai, M.D., and Jay H. Krachmer, M.D.

Over a 14-year period from 1974 to 1988, 12 eyes of 11 patients with pellucid marginal corneal degeneration underwent penetrating keratoplasty. Peripheral corneal thinning required a large eccentric graft in each case. Follow-up ranged from one to eight years (mean, three years). One graft failed because of a persistent epithelial defect with keratolysis of the wound. Although endothelial allograft rejection was common, occurring in seven of 11 (64%) clear grafts, no graft failed because of rejection. Other complications included retinal detachment and a bacterial corneal ulcer. Suture erosion and vascularization of the graft were not problems. Postoperative spectacle correction was dispensed an average of 11 months after surgery. Visual acuity in seven patients without amblyopia, retinal disease, or a previous corneal ulcer at the time of spectacle correction ranged from 20/20 to 20/40 (mean, 20/30). Average final keratometric astigmatism in these patients was 2.46 diopters (range, 0.00 to 5.25 diopters). We believe that penetrating keratoplasty offers an excellent surgical result for patients with pellucid marginal corneal degeneration.

PELLUCID MARGINAL CORNEAL DEGENERATION is an ectatic corneal condition characterized by thinning of the inferior peripheral cornea.[1] This bilateral condition typically occurs with no sex predilection in patients who are 20 to 40 years of age. The thinned area, located 1 to 2 mm from the inferior corneoscleral limbus, is 1 to 2 mm in width, and characteristically extends from the 4 o'clock to the 8 o'clock meridians.

The cornea above this thinned area protrudes, which flattens the vertical meridian and creates large against-the-rule (axis near 180 degrees) irregular astigmatism. Inferiorly, over the ectatic area, the vertical meridian steepens. This creates significant inferior steepening.[2] In exceptional cases, the thinning can extend superiorly to include the horizontal meridian. If this occurs, vertical flattening can be balanced by horizontal flattening, which results in less overall astigmatism.

As the topographic changes progress, spectacle correction of vision becomes impossible. Although rigid contact lenses may improve vision, the inferior nature of this disorder and severe astigmatism create difficulty in obtaining an adequate fit. Often these patients require surgical intervention to improve vision.

A number of surgical procedures for visual rehabilitation of patients with pellucid marginal corneal degeneration have been described. These included thermocauterization, diathermy, crescentic lamellar keratoplasty,[3] crescentic penetrating keratoplasty,[4] and large eccentric penetrating keratoplasty.[2,4-9] Reported results consisted only of isolated cases with limited follow-up. Since the thinned area is close to the inferior corneoscleral limbus, penetrating keratoplasty requires a large inferiorly displaced graft. These grafts, placed near the limbal vasculature, have an increased risk of vascularization and subsequent transplant rejection. Additionally, higher postoperative astigmatism may result from an eccentric graft. The present series includes the results of large eccentric penetrating keratoplasty in 12 eyes of 11 patients with pellucid marginal corneal degeneration.

Patients and Methods

All charts of patients undergoing penetrating keratoplasty from 1974 to 1988 for pellucid marginal corneal degeneration were reviewed.

Each patient was examined by one of us (J.H.K.). Patients were excluded if follow-up was less than one year. The diagnosis of pellucid marginal corneal degeneration was made by slit-lamp examination. All patients had characteristic inferior stromal thinning with protrusion above the thinned area. The inferior location as well as an absence of vascularization or lipid deposits helped to distinguish pellucid marginal corneal degeneration from Terrien's peripheral corneal degeneration. The diagnosis of pellucid marginal corneal degeneration coexisting with keratoconus was made by finding two separate and distinct areas of corneal thinning. The thinning associated with keratoconus was greatest at the apex of the cone. The inferior thinning secondary to pellucid marginal corneal degeneration occurs inferior to the corneal protrusion (Figure). These two areas of thinning are separated by cornea of more normal stromal thickness. These patients were included because the major factor determining the size and location of the corneal transplant was the extent and location of the inferior thinning secondary to pellucid marginal corneal degeneration. The keratoconic area was thus always included in the host tissue removed at surgery. Preoperative vision of all patients undergoing penetrating keratoplasty was either inadequate

or the patient was intolerant of the spectacle correction or contact lens fit.

All but one patient underwent only a penetrating keratoplasty. The exception was a 71-year-old woman who had an intracapsular cataract extraction at the time of corneal transplantation. Most grafts were 9.0 or 9.5 mm in the same size recipient bed. One graft was 10.0 mm and one graft was 0.5 mm larger than the recipient bed. In all cases, the grafts were inferiorly displaced to encompass the abnormal cornea. Most grafts were secured with interrupted 10-0 nylon sutures. The exceptions (in two cases) were secured with a single running suture or a combination of interrupted and running sutures.

Sutures were removed if they were loose or eroded or for modification of astigmatism when the wound was stable. Location of suture removal or vascularization was indicated by a drawing or by noting the clock hour. Postoperative visual acuity and astigmatism were recorded at the time spectacle correction was given. Mean visual acuity is calculated from the Snellen visual acuity converted to a decimal number.

Results

A study of patients undergoing penetrating keratoplasty disclosed 12 eyes of 11 patients with pellucid marginal corneal degeneration and at least one year of postoperative follow-up. Seven (64%) patients were men, and four (36%) were women. There were five right and seven left eyes. Patients ranged in age from 29 to 71 years. Coexisting conditions included cataracts, amblyopia, Down's syndrome, keratoconus, and hydrops. Of these eyes, eight (67%) also had features of keratoconus.

The average postoperative follow-up was three years (range, one to eight years). Although two patients were lost to follow-up an average of five years after surgery, the remainder continue to be followed up. Ten of the 12 grafts were clear at the patients' last visit. One patient with Down's syndrome and trichiasis developed a postoperative bacterial corneal ulcer that responded to appropriate antibiotics. However, a resultant paracentral scar limited postoperative vision. The only case of graft failure occurred in a healthy 40-year-old man who had a successful graft in his fellow eye. The original graft was repeated at one month because of persistent epithelial defects and ker-

Keratoconus ——

Pellucid
Marginal
Degeneration
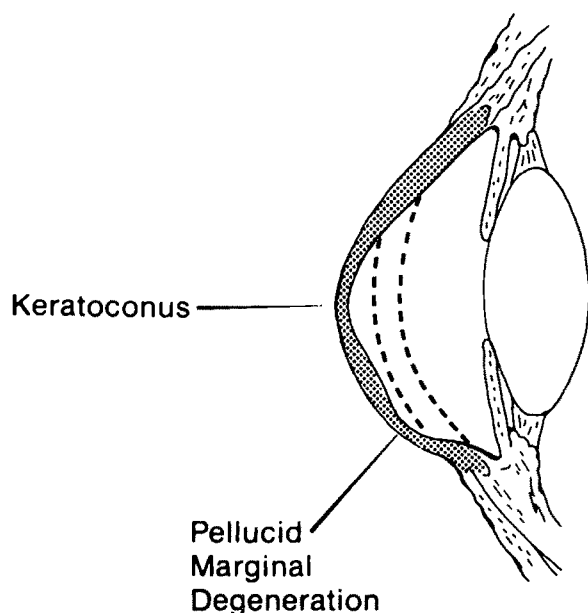
Figure (Varley, Macsai, and Krachmer). Inferocentral thinning and protrusion characteristic of keratoconus as well as inferior thinning characteristic of pellucid marginal corneal degeneration are shown.

atolysis of the wound. Repeated grafts had similar difficulties. The most recent graft is clear, but postoperative vision is limited by a cataract.

Other complications included wound leak, mild increase of intraocular pressure, endothelial allograft rejection, and a retinal detachment. The wound leak was easily repaired by a minor operation. Increased intraocular pressure occurred in only one patient. It was controlled with a single medication. Although seven of 11 clear grafts (64%) had at least one endothelial allograft rejection episode, no graft failed secondary to a rejection. The retinal detachment occurred in a patient who had a combined penetrating keratoplasty and intracapsular cataract extraction. Despite successful repair of the retinal detachment, final vision was limited by a retinal abnormality.

Sutures were removed when loose or to modify astigmatism when the wound was stable. Although loose, eroded sutures did occur, this appeared to be random and was not isolated to the inferior wound where the graft is closest to the corneoscleral limbus. Additionally, eroded sutures were removed without complication.

Superficial vascularization of the graft occurred in four eyes. In each case, it was not progressive and did not interfere with vision. The location appeared random and was not more common inferiorly. Only in the failed graft, in which vascularization occurred around the circumference, was it a problem. In this patient, repeat penetrating keratoplasty was performed in a vascularized cornea.

Astigmatism, refraction, and visual acuity were recorded at the time of visual correction. This ranged from six to 21 months (mean, 11 months) after surgery. Average postoperative keratometric astigmatism was 2.46 diopters. One patient required relaxing incisions with augmentation sutures for 9 diopters of postkeratoplasty astigmatism. The patient responded well with final keratometry of 40.00/40.00. Visual acuity in seven patients not limited by retinal disease, amblyopia, or previous microbial keratitis ranged from 20/20 to 20/40. Average visual acuity in these patients was slightly better than 20/30.

Discussion

Minimum follow-up was one year and averaged three years. Coexisting conditions seen in our patients, such as corneal hydrops (one eye)

and Down's syndrome (one eye), are well recognized and have been previously reported.[5,10] Although less well recognized, the coexistence of keratoconus and pellucid marginal corneal degeneration, seen in eight of the eyes, has also been previously reported.[10]

Since the thinned portion of the cornea is 1 to 2 mm from the inferior corneoscleral limbus, a penetrating keratoplasty must be inferiorly displaced to encompass the thinned cornea or so large that virtually all of the cornea is replaced. Even when inferiorly displaced, these grafts were larger than normal to avoid sutures encroaching on the visual axis superiorly. Typically, grafts were 9.0 or 9.5 mm with the same size recipient bed. Despite the close proximity of the graft to the corneoscleral limbus, early suture erosion and vascularization of the graft occurred randomly around the graft and were not isolated to the inferior wound.

The use of penetrating keratoplasty in the management of pellucid marginal corneal degeneration has been reported.[2,4-9] However, reports include isolated cases of patients with limited follow-up data. Parker and associates[4] summarized two cases in their report of the clinicopathologic features of pellucid marginal corneal degeneration. In the first case, the patient had four episodes of allograft rejection within the first two years, but at five years after surgery visual acuity was 20/30 with a clear central graft. In the second, the patient had a clear graft with 20/60 visual acuity 18 months after surgery. Carter, Jones, and Wilhelmus,[6] in their communication on acute hydrops occurring in pellucid marginal corneal degeneration, described a patient with 20/30 visual acuity after penetrating keratoplasty and a successfully treated allograft reaction. Speaker, Arentsen, and Laibson[8] reported the survival of large diameter penetrating keratoplasties. Two eyes of 15 patients were transplanted for pellucid marginal corneal degeneration. Despite an increased prevalence of graft rejection, they documented a good prognosis for these large grafts.

Endothelial allograft rejection was common in our patients as well. At least one rejection episode occurred in seven of 11 (64%) of our clear transplants. When corneal edema occurred with a rejection episode, it was most often located inferiorly where the graft is in proximity to the corneoscleral limbus. All rejections responded quickly to topical and systemic corticosteroids, and no graft failed secondary to rejection. Even so, an incidence of 64% is higher than that reported for keratoconus grafts (7%

to 38%). Therefore, these patients require careful follow-up and repeated instructions to report symptoms early.

In a small series such as this, it is difficult to comment on the frequency of complications. With the exception of allograft rejection, however, no other complication stood out as being excessive. Additionally, early suture erosion or stromal vascularization did not complicate the postoperative course in these patients.

Eliminating two patients with retinal disease (previous retinal detachment and macular degeneration), one patient with amblyopia, and one patient with a corneal scar, postoperative visual acuity ranged from 20/20 to 20/40. These visual results are similar to those seen after penetrating keratoplasty for keratoconus (92% equal or better than 20/40).[11-13] Visual correction was dispensed an average of 11 months after surgery. Since these grafts are larger and, therefore, closer to the corneoscleral limbus, it is possible that the wound heals quicker, which allows for earlier suture removal for modification of astigmatism.

Keratometric astigmatism in all clear grafts at the time of visual correction averaged 2.46 diopters. This is slightly better than the reported postoperative astigmatism in keratoconus patients (3.8 to 4.1 diopters).[12,13] Although this astigmatism was stable at the time spectacles were given, in some patients with residual sutures in place it may change as sutures break and are removed. Additionally, one patient did require surgical correction of 9.0 diopters of postkeratoplasty astigmatism. The patient responded well to relaxing incisions with augmentation sutures as previously described.[14]

We believe that a large eccentric penetrating keratoplasty offers an excellent surgical correction for pellucid marginal corneal degeneration. Early suture erosion and graft vascularization were not problems. Visual results are similar to those reported for keratoconus. Although allograft reactions are common, if diagnosed early and treated aggressively they respond well.

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Enchondromatosis and Hemangioma (Maffucci's Syndrome) With Orbital Involvement

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Maffucci's syndrome is a rare, congenital disease of unknown cause characterized by the development of multiple enchondromas and soft-tissue hemangiomas. We treated a 34-year-old man with Maffucci's syndrome, bilateral proptosis secondary to multiple intraorbital hemangiomas, corneal exposure secondary to a left facial nerve palsy, and multiple intra-abdominal tumors. The skeletal manifestations were not clinically apparent and were only discovered after a careful radiologic survey. Simultaneous bilateral orbital cavernous hemangiomas should alert the physician to the possibility of Maffucci's syndrome.

CAVERNOUS HEMANGIOMA has been described as the most common primary orbital tumor in adults.[1] Most patients have unilateral solitary lesions, although multiple lesions have been found to involve the same orbit. Harris and Jakobiec[2] analyzed 66 cases of orbital cavernous hemangioma and found no cases of bilateral orbital involvement. Unilaterality is usually the rule, although one case of bilateral simultaneous cavernous hemangioma has been documented.[3] We treated a patient with multiple tumors that were consistent with cavernous hemangiomas in both orbits and the clinical features of Maffucci's syndrome.

Case Report

A 34-year-old man had bilateral, painless proptosis for six years with associated left-sided hearing loss, multiple swellings involving his face, neck, back, shoulders, and arms, and abdominal pain. Previous treatment included a left external carotid ligation three years previously for unknown reasons. The results of a biopsy of a neck lesion two years later showed cavernous hemangioma. The patient's medical history was otherwise unremarkable, and the family history was noncontributory.

On examination the best-corrected visual acuity was R.E.: 20/25 and L.E.: light perception with poor projection. Bilateral axial proptosis was noted, and Hertel exophthalmometer readings with a 105-mm base disclosed 29 mm for the right eye and 31 mm for the left eye. The results of the anterior segment examination of the right eye showed only slight conjunctival hyperemia. The left eye, however, demonstrated evidence of marked corneal exposure with secondary keratinization of the cornea and conjunctiva (Fig. 1). A left-sided seventh nerve palsy and severe sensorineural hearing loss were detected. The right eye was normal; however, visualization of the left fundus was not possible because of corneal opacification. Multiple subcutaneous nodules of various sizes were palpable on the patient's face, neck, back, shoulders, and arms (Fig. 2). Additionally, bony prominences were evident on the left side of his skull, yet no other gross skeletal abnormalities were noted. The thyroid was not enlarged.

The results of laboratory investigations disclosed normal values for the following: complete blood cell count, urinalysis, electrolytes, serum calcium, phosphorus, blood urea nitrogen and creatinine levels, liver function studies, thyroid function studies, serum cortisol, serum protein electrophoresis, and antibody test for human immunodeficiency virus.

Skull x-rays indicated multiple areas of destructive changes in the vault and base of the skull. Involvement was mostly on the left side of the calvarium, including the occiput, parietal, and frontal bones. The changes extended into the left sphenoid bone, the sphenoid sinus,

Fig. 1 (Johnson and associates). A 35-year-old man with bilateral axial proptosis, left seventh cranial nerve palsy, and resultant exposure keratitis with keratinization of the left cornea and conjunctiva.

and posterior ethmoid sinuses. The sella turcica appeared to be completely destroyed (Fig. 3).

Skeletal x-rays displayed multiple, radiolucent areas consistent with enchondromas within the proximal two thirds of the third, fourth, and fifth right metacarpal bones (Fig. 4). Similar lesions were seen in the proximal right radius and ulna, the right humerus, the left radius, and in both fibulas. No abnormalities were interpreted from plain x-rays of the spine, pelvis, feet, knees, and chest.

Computed tomographic scans of the orbits and brain disclosed multiple, well-delineated round and oval tumors within both orbits. These varied in size from a few millimeters to 20 mm in diameter (Fig. 5). The lesions enhanced strongly after intravenous contrast injection. Tumor extension was noted through the left optic canal and left superior orbital fissure with involvement of the middle cranial fossa and left cavernous sinus. There was extensive involvement of the left temporal bone, sphenoid bone, left part of occipital bone, and focal areas of both parietal and frontal bones, with a partially osteolytic and partially osteoblastic tumor (Fig. 6). On the inside of the skull, the bony changes were lined with an irregular layer of contrast-enhancing soft tissue, which extended near the foramen magnum up to the tentorium and supratentorially along the petrous bone. A few similar, soft-tissue mass lesions were seen along the inner table of the skull (Fig. 7).

Computed tomographic scans of the abdomen displayed an irregular, hypodense area measuring 5 × 3 cm in the anterolateral part of the right liver lobe, slightly beneath the right

Fig. 2 (Johnson and associates). Profile of the patient shows marked, left-sided proptosis as well as multiple, subcutaneous nodules involving the left side of the face.
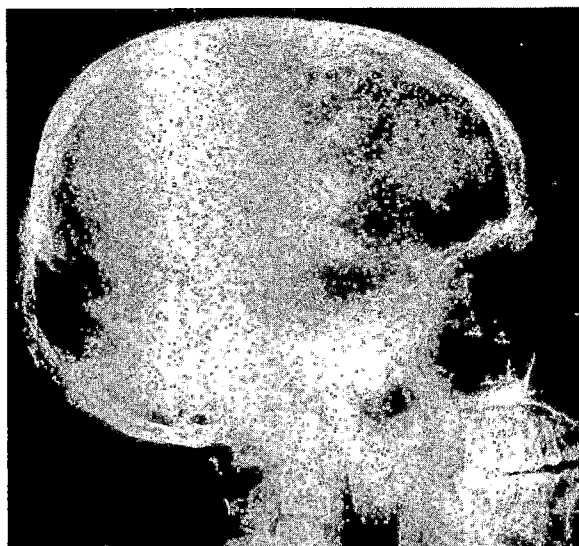
Fig. 3 (Johnson and associates). Skull x-ray showing multiple areas of destructive change in vault and base of skull, and destruction of the sella turcica.

Fig. 4 (Johnson and associates). Right hand x-ray displays multiple, radiolucent areas within proximal two thirds of third, fourth, and fifth metacarpals, consistent with enchondromas (arrows).

Fig. 5 (Johnson and associates). Nonenhanced computed tomographic scan shows multiple, well-delineated, round to oval tumors within both orbits of varying sizes. Tumor extension is evident through superior orbital fissure, with involvement of left middle cranial fossa and cavernous sinus.

hemidiaphragm, with smaller, rounded, radiolucent areas scattered throughout the liver. The spleen was enlarged and also showed multiple radiolucent lesions. Large, rounded, partly lobulated tumor masses were found in the area of both adrenal glands. These had minimal peripheral calcifications with a slight rim enhancement after contrast.

The results of ultrasound assessment of both orbits, the skull lesions, and the facial masses disclosed multiple, well-outlined, spherical masses in both orbits with high internal reflectivity, multiple cavernous spaces, and minimal vascularity. The skull and facial lesions had similar echographic characteristics, and there was mild attenuation of the sound beams in all lesions. The findings of the orbital, skull, and facial lesions were echographically consistent with cavernous hemangiomas[4] (Figs. 8 and 9).

The results of a biopsy of a subcutaneous nodule from the left cheek showed large, vascular lumens with thick, fibrous walls and a single layer of mature endothelium. Many of the vascular cavities contained erythrocytes (Fig. 10). Cavernous hemangioma was diagnosed, and the diagnosis of Maffucci's syndrome was suggested by one of us (R.M.N.), based on the

history, clinical findings, and histopathologic findings. Biopsy specimens were also obtained from the left parieto-occipital skull. Soft-tissue biopsy specimens showed cavernous hemangioma (Fig. 11), whereas bone biopsy specimens demonstrated no abnormalities.

After the initial examination the patient was transferred to an oncology center for further investigation of the intra-abdominal tumors. The patient left the hospital despite medical advice and has been lost to follow-up.

Discussion

The syndrome of multiple enchondromas combined with multiple soft-tissue hemangiomas was first described by Maffucci at the University of Naples in 1881.[5] The syndrome is
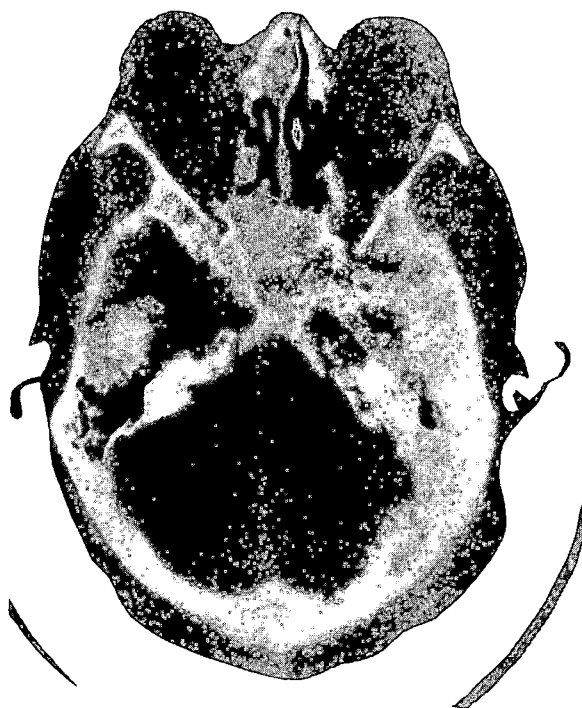
Fig. 6 (Johnson and associates). Bone window setting of enhanced axial computed tomographic scan illustrates marked destructive changes within the base of the skull.

Fig. 7 (Johnson and associates). Enhanced axial computed tomographic scan illustrates marked contrast enhancement of orbital lesions, bony changes in skull bones, and contrast-enhancing soft-tissue lesion adjacent to bony abnormalities within the posterior and middle cranial fossae.

characterized by both skeletal and nonskeletal manifestations.

The skeletal changes are believed to be caused by a congenital defect in endochondral ossification that affects the growing ends of bones and results in irregular growth (dyschondroplasia). Islands of cartilage may begin to proliferate or come to the surface, forming expanding cartilaginous tumors (enchondromas).[6]

The lesions most commonly involve the metacarpals and phalanges of the hands and the bones of the feet, and frequently involve the tibia, fibula, radius, and ulna.[7,8] Tumors have also been reported to involve vertebrae, ribs, scapula, pelvis, and skull.[6,9] Cranial nerve palsies have been described as the cause of involvement of the base of the skull.[10] The skeletal manifestations usually occur in early or midchildhood, and tumor growth usually ceases by the end of the second decade.[6-8] Often the lesions are asymmetric, but they are rarely unilateral.[11] Fractures of affected bones may follow minimal trauma; this occurred in 26% of the patients in Anderson's review of 62 reported cases.[6] The patients are often of short stat-

ure, and the limbs are often deformed as a result of a malunion of fractures.[6,8,12] The dyschondroplasia in Maffucci's syndrome does not differ from that in multiple enchondromatosis or Ollier's disease.[11,13]

The nonskeletal manifestations of Maffucci's syndrome consist primarily of simple or cavernous hemangiomas occurring in the subcutaneous tissues and occasionally involving the viscera.[6,7] The tumors usually are noted in infancy, involve the limbs, and vary greatly in size.[6] Thrombosis in dilated vessels and phlebectasia are common findings.[6,7] Patients may have orthostatic hypotension secondary to pooling of blood in dependent hemangiomas.[9] Cutaneous lymphangiomas have also been associated with this syndrome,[10] as well as skin pigmentation abnormalities including hyperpigmentation, nevi, and vitiligo.[6]

A generalized predisposition to neoplasia in adulthood has been well established in Maffucci's syndrome. Malignant transformation of enchondromas to chondrosarcomas has been noted in 15% to 20% of patients.[8,9,12] Malignant degeneration of hemangiomas and lymphangiomas may also occur.[7] Other tumors reported to be associated with this syndrome include fibrosarcoma, glioma, mesenchymal ovarian tumor, carcinoma of the pancreas, pituitary adenoma,
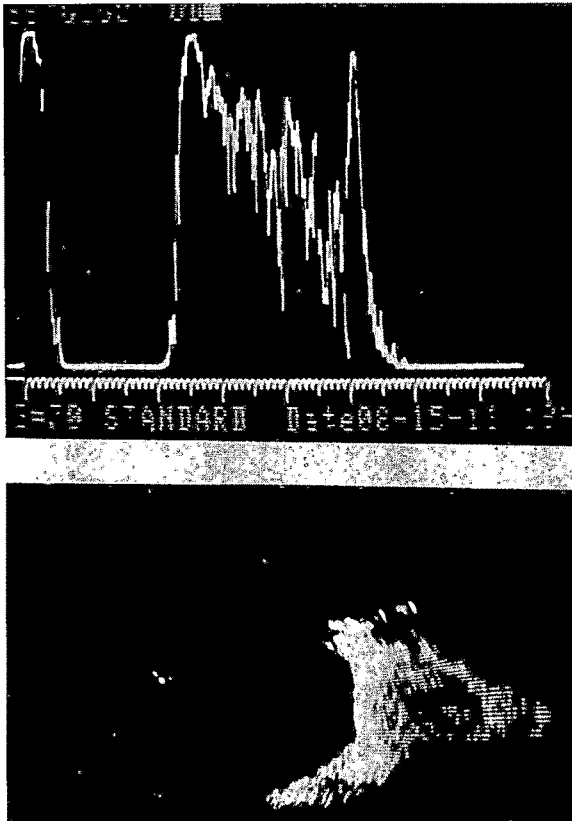
Fig. 8 (Johnson and associates). Composite echogram of orbital lesions. Top, A-scan showing high reflective, well-encapsulated, solid lesion with multiple septa and moderate sound attenuation. Bottom, B-scan showing rounded, retrobulbar mass. These findings are typical of cavernous hemangiomas.
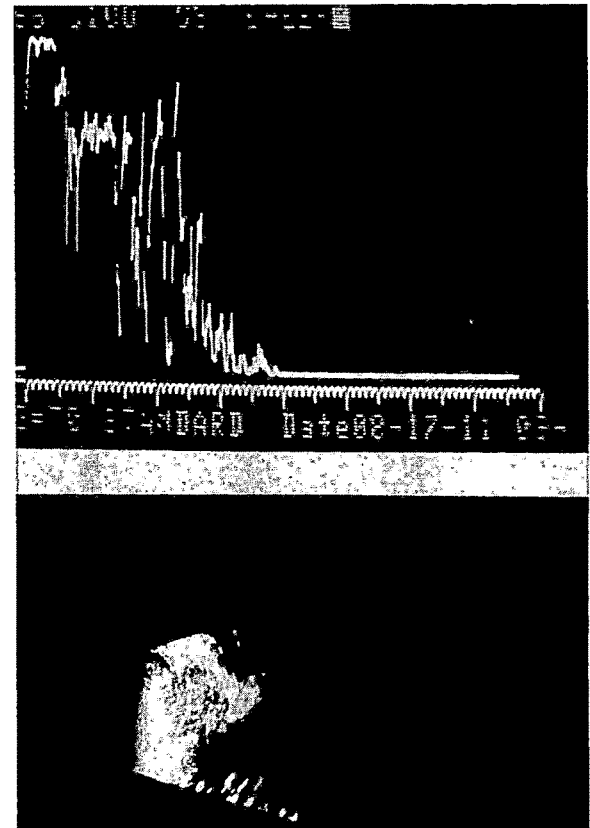
Fig. 9 (Johnson and associates). Composite echogram of facial lesion. Top, A-scan showing multiple, well-encapsulated, septated lesions with moderate sound attenuation. Bottom, B-scan showing spherical mass with multiple echolucent areas. These findings are consistent with cavernous hemangioma.

uterine polyp, uterine fibroid, adrenal cortical adenoma, ovarian thecoma, multiple fibromas,[8] and adenocarcinoma of the liver.[12]

Men and women are affected equally and there is no racial predilection.[6-9] The disease is congenital but not hereditary.[6,8] Patients are usually of normal intelligence[8,9] with normal karyotypes.[6,9,10] The cause of the disease is unclear. The syndrome appears to represent a congenital mesodermal dysplasia with frequent mesodermal neoplasia.[6,8] The complete syndrome, in which patients exhibit gross deformities, is exceedingly rare. Many mild cases and formes frustes are usually not diagnosed.[6]

Other diseases considered in the differential diagnosis include Klippel-Trénaunay-Weber syndrome and blue rubber bleb nevus. Patients with Klippel-Trénaunay-Weber syndrome develop varicosities of the legs, cutaneous hemangiomas, and hypertrophy of tissues in the af-

fected limbs.[14] A congenital varix of the forehead and inferior orbital vein resulting in intermittent exophthalmos has been documented in a patient with this syndrome.[15] This disease is usually unilateral, unlike Maffucci's syndrome, and the affected limb is enlarged, warmer, and elongated, compared to that of the unaffected side.[9]

Blue rubber bleb nevus syndrome is an autosomal dominant disorder characterized by blisterlike, compressible, vascular nevi both on the body surface and involving the viscera.[16] The nevi are often painful, and the disease is associated with gastrointestinal bleeding.[17] Intermittent exophthalmos from a presumed orbital vascular malformation has been reported in association with this syndrome.[18]

Ophthalmic manifestations in Maffucci's syndrome are observed rarely. Facial hemangiomas, retinal hemorrhages, and papilledema

Fig. 10 (Johnson and associates). High-power view of cheek cavernous hemangioma demonstrates large vascular lumens with thick, fibrous walls lined with a single layer of mature endothelium (hematoxylin and eosin, × 100).
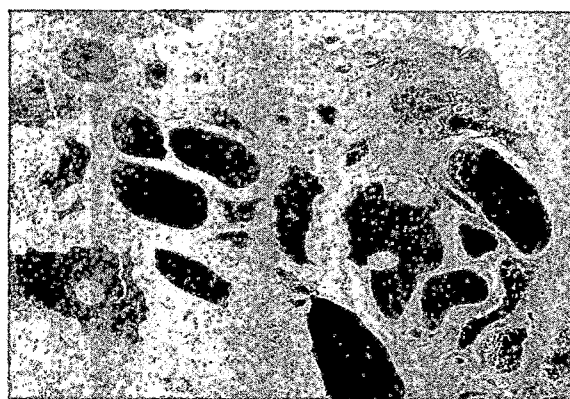
Fig. 11 (Johnson and associates). Low-power view of cavernous hemangioma of scalp exhibiting large, blood-filled vascular lumens and thick, fibrous septa (hematoxylin and eosin, × 20).

secondary to an intracranial tumor have been reported.[19] Loewinger and associates[10] described an 18-year-old woman with Maffucci's syndrome who had a large, intracranial tumor compatible with either an osteochondroma or chondrosarcoma, multiple cranial nerve palsies, and a progressive, right proptosis. A brain scan was "suggestive of an haemangioma in the right retro-orbital region." Our patient had bilateral proptosis secondary to multiple cavernous hemangiomas and clinical findings of Maffucci's syndrome. The identical echographic and radiologic findings of the orbital, facial, and skull masses suggest a similar internal structure and histopathologic nature.[20] Echographic characteristics are known to be a direct reflection of the internal structure of tissues and are specific in differentiating lesions such as cavernous hemangiomas. The diagnosis of facial and skull cavernous hemangiomas suggests the orbital lesions are similarly cavernous hemangiomas. Previous echographic and histopathologic correlations made on tumors support the concept of standard correlations of tissues based on similar echographic and radiologic findings.[21,22] The long bone abnormalities in this patient were found after a careful radiologic survey. They were not clinically apparent.

Treatment of the manifestations of this syndrome is surgery, with orthopedic or general surgical intervention required for correction of deformities and, occasionally, amputations of grossly deformed limbs and digits.[6,8,9] Irradiation has been used in an attempt to reduce the size of hemangiomas, but the benefits are questionable and the modality is not recommend-

ed.[8] Careful and prolonged follow-up is essential to detect malignant transformation of tumors.[6,7] When chondrosarcomas develop, the prognosis is poor.[11,12]

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OPHTHALMIC MINIATURE

"I understand you're a doctor?"

"I'm an ophthalmic surgeon."

. . . "Did I ever tell you what—no, I didn't. It was one of the ladies-in-waiting. I never did find out what they were waiting for. Anyway, this one countess . . . she was right out of Gone With the Wind," Cathy said with a chuckle. It was his wife's favorite epithet for useless women. "She asked me if I did needlepoint."

Not the sort of thing you ask my wife. Jack grinned at the windows. "And you said . . ."

"Only on eyeballs." A sweet, nasty smile.

Tom Clancy, *Patriot Games*
New York, Berkley Books, 1987, pp. 116 and 161

Treatment of Manifest Latent Nystagmus

Alina A. Zubcov, M.D., Robert D. Reinecke, M.D., Irene Gottlob, M.D.,
Donelson R. Manley, M.D., and Joseph H. Calhoun, M.D.

Eight patients with manifest latent nystagmus, as noted by ocular movement recordings, were examined for nystagmus reduction after surgical or optical treatment. Seven of the patients had strabismus. Five patients underwent strabismus surgery, had no tropia postoperatively, and the manifest latent nystagmus converted to latent nystagmus. Four of these five patients subsequently showed improvement in binocular visual acuity. Three patients received optical treatment; one had accommodative esotropia and, with appropriate spectacle correction, the manifest latent nystagmus was converted to latent nystagmus with improved vision. In the other two patients the manifest latent nystagmus lessened after correction with appropriate spectacles; binocular visual acuity of one of these patients improved. The possibility of converting manifest latent nystagmus to latent nystagmus by strabismus surgery is a reasonable surgical goal. In patients with manifest latent nystagmus and strabismus, surgical or optical alignment of the eyes decreases the nystagmus intensity and may also improve binocular visual acuity.

MANIFEST LATENT NYSTAGMUS is a congenital jerk form of nystagmus in which the fast phase

is toward the fixating eye and the slow phase has decreasing velocity. It occurs when viewing binocularly (with both eyes open) but fixating monocularly.

Latent nystagmus is identical to manifest latent nystagmus in wave form and differs only in its manifestation. True latent nystagmus occurs when covering or blurring the image in one eye; it is absent when viewing with both eyes. Latent nystagmus is always present in patients with manifest latent nystagmus. It has been shown that strabismus is necessary for manifest latent nystagmus, since patients with strabismus typically fixate monocularly while viewing with both eyes. This is presumably caused by cortical suppression.[1]

Binocular visual acuity in patients with latent nystagmus is one to several lines better than the monocular visual acuity of either eye.[2] Through its characteristic wave form with minimal foveation time per cycle, manifest latent nystagmus and latent nystagmus are reported to be correlated with a poorer visual acuity than other wave forms or types of nystagmus.[3,4]

We investigated methods of reducing nystagmus and improving binocular visual acuity in patients with manifest latent nystagmus. In patients with latent nystagmus, binocular visual acuity was better when the nystagmus intensity decreased.[2] One case with documented ocular movement recordings preoperatively and postoperatively has been reported.[5] The patient had heterotropia and manifest latent nystagmus that converted into latent nystagmus after successful surgical alignment of the eyes. No data on binocular postoperative visual acuity, however, were given.

We treated eight patients in whom we performed ocular movement recordings. In six patients the manifest latent nystagmus converted to latent nystagmus, and two patients had reduced manifest latent nystagmus after successful strabismus surgery or optical alignment of the eyes. Six of the eight patients also demonstrated improved binocular visual acuities.

Patients and Methods

All of the patients had manifest latent nystagmus, reliable visual acuity measurements, and all received treatment. The criteria for entering the study were based on the patients' initial ocular movement recording done at the Foerderer Eye Movement Center for Children. The electro-oculographic criteria proposed by Dell'Osso, Schmidt, and Daroff[6] and Dell'Osso[7] were used to differentiate between manifest latent nystagmus, latent nystagmus, and infantile nystagmus wave forms. The manifest latent nystagmus and latent nystagmus were characterized by a typical wave form: a fast jerk followed by a slow phase decreasing in velocity. In contrast, the pendular wave form, a jerk wave form with increasing velocity of the slow phase, and triangular and torsional wave forms were thought to be consistent with infantile nystagmus. The presumed foveation time was measured as the period of time during which the ocular movement velocity was less than 2.5 degrees per second.[8] Nystagmus intensity was defined as the nystagmus amplitude multiplied by its frequency.

Eight patients met the criteria and were followed up for a mean of 1.75 years. Within this interval they were examined two to four times and treated by one of us.

At least one complete ocular examination and ocular movement recording was done before treatment and one was done shortly after treatment. Binocular visual acuities were measured in primary position and in the preferred head position, if different. Monocular visual acuities were measured by two techniques: with full occlusion of the fellow eye and while holding a +4.00 spheric lens in front of the fellow eye. If the patient could not give subjective visual acuity responses, sweep visual-evoked cortical potentials were used to estimate visual acuity quantitatively.[9] The visual acuity measurements were obtained between six and 16 weeks apart. No therapy for amblyopia was received by any of the patients within the intervening period. All patients' ocular movements were recorded on videotape at each visit. The amplitude of the nystagmus was estimated in percentage of the corneal diameter from the television tape recordings for gain standardization of the infants who had electro-oculograms. The accuracy of the estimate was ±0.25 mm.

The ocular movement recordings were done with a scleral, magnetic search coil system or electro-oculogram. The electro-oculography system used a Tracor RV-275 recorder and the method described by Reinecke, Guo, and Goldstein.[10] The scleral search coil recording system has been described by Collewijn, van der Mark, and Jansen.[11] The ocular movements were recorded over a period of three to five minutes in the straight-ahead position and in different fields of gaze with both eyes open and with each eye sequentially covered. As much as cooperation permitted, ocular movements elicited by near and far targets were recorded. In one patient (Case 8), a torsional coil recording was also performed. The proportion of occurrence of different nystagmus wave forms was estimated relative to the overall recording time.

Results

The clinical and ocular movement data of our patients are given in the Table.

Case 1

A 7-month-old boy had constant nystagmus and 50 prism diopters of esotropia. The wave form analysis by electro-oculography disclosed 70% manifest latent nystagmus wave form and 30% infantile nystagmus wave form (pendular) with 20- to 40-msec foveation time per cycle (Fig. 1). Visual acuity with both eyes open (by sweep visual-evoked potential) recorded at the age of 7 months was estimated to a Snellen equivalent of 20/50. Shortly after successful ocular muscle surgery, the Brückner test disclosed orthophoria. On electro-oculography only the pendular wave form of infantile nystagmus was recorded when both eyes were open (Fig. 2). The frequency of the nystagmus did not change (3 Hz), whereas the foveation time per cycle increased to between 60 and 120 msec. The amplitude of the nystagmus, as measured in percentage of the cornea diameter from the television tape recordings, also was constant. With either eye covered, the latent nystagmus was obvious. Binocular visual acuity, by sweep visual-evoked potential, was estimated to a Snellen equivalent of 20/40, which showed a modest increase.

Case 2

A 6-year-old boy who had nystagmus since infancy developed a left head turn over the past

TABLE
CLINICAL DATA OF EIGHT PATIENTS WITH NYSTAGMUS*

CASE NO., AGE (YRS)	DIAGNOSIS	PRETREATMENT BINOCULAR VISUAL ACUITY	TREATMENT	POSTTREATMENT CLINICAL FINDINGS	BINOCULAR VISUAL ACUITY
1, 0.58	Infantile esotropia, nystagmus, myopia, anisometropia	20/50 (sweep VEP)	Bimedial rectus recession	Orthophoria, latent nystagmus	20/40 (sweep VEP)
2, 6	Infantile esotropia, right hypertropia, nystagmus, left head turn and tilt	20/40 (left head turn)	Horizontal Kestenbaum procedure	Orthophoria, latent nystagmus	20/25
3, 57	Acquired A pattern exotropia, nystagmus, oscillopsia	20/80	Bilateral superior oblique tenotomies	Orthophoria	20/30
4, 6	Infantile esotropia, left dissociated vertical deviation, nystagmus, status postbimedial rectus recession	20/40 (before last surgery)	Left medial rectus recession, left superior rectus recession	Orthophoria, occasionally 12 P.D. left dissociated vertical deviation	20/30
5, 12	Infantile esotropia, dissociated vertical deviation in both eyes, nystagmus; status postbimedial rectus recession	20/25 (before last surgery)	Inferior rectus resection	Orthophoria	20/25
6, 5	Accommodative esotropia (variable), nystagmus	20/70 (Allen cards)	Correction of hyperopia	Orthophoria, 5 P.D. exophoria, right head turn	20/38 (sweep VEP), 20/40 (tumbling E)
7, 14	2–4 P.D. esotropia, 4 P.D. dissociated vertical deviation in both eyes, status postbimedial rectus recession and bilateral rectus recession, myopia, nystagmus	20/60	Correction of myopia	Unchanged	20/60
8, 12	Orthophoria, myopia, torsional and horizontal nystagmus, stationary night blindness, right head tilt	20/50	Correction of myopia	Unchanged	20/30

*VEP indicates visual-evoked potential, and EOG indicates electro-oculogram.

year. The patient had had ocular muscle surgery for infantile esotropia. At his preferred head position of 30 degrees to the left, binocular visual acuity was 20/40. In primary position he had approximately 64 P.D. of esotropia with

4 to 6 P.D. of right hypertropia. The electro-oculography disclosed 20% of infantile nystagmus wave form (pendular) with a null point at 20 degrees right gaze and 80% of manifest latent nystagmus wave form (Fig. 3). After suc-

TABLE *(continued)*
CLINICAL DATA OF EIGHT PATIENTS WITH
NYSTAGMUS*

OCULAR MOVEMENT RECORDINGS

PRETREATMENT	POSTTREATMENT
30% infantile nystagmus wave form (pendular) and 70% manifest latent nystagmus wave form (EOG)	Infantile nystagmus wave form (pendular) and latent nystagmus (EOG)
80% manifest latent nystagmus, 20% infantile nystagmus wave form (EOG)	Virtually no nystagmus in primary position, latent nystagmus (EOG)
Manifest latent nystagmus wave form (magnetic search eyecoil)	Latent nystagmus (magnetic search eyecoil)
Manifest latent nystagmus	Latent nystagmus (EOG)
Manifest latent nystagmus	Latent nystagmus (EOG)
Manifest latent nystagmus wave form and intermittent pendular nystagmus at 8 Hz (EOG)	Latent nystagmus, intermittent pendular nystagmus at 8 Hz (EOG)
Manifest latent nystagmus wave form at 2.5 Hz and 1 degree (magnetic search eyecoil)	Manifest latent nystagmus at 1 Hz and .5 degrees (magnetic search eyecoil)
Manifest latent nystagmus at 2.5 Hz (EOG) and torsional nystagmus (torsional coils)	Manifest latent nystagmus at 1.5 Hz (magnetic search eyecoil) and torsional nystagmus

cessful Kestenbaum-type ocular muscle surgery (bilateral horizontal recti recess-resect to reposition null point), the patient had orthophoria at distance by alternate cover test with virtually no nystagmus present in primary position either clinically or in ocular movement record-

ings. When covering either eye, latent nystagmus was still present (Fig. 4). Binocular visual acuity increased to 20/25. Postoperatively, the patient developed a right head tilt of 15 degrees.

Case 3

A 57-year-old man had an A pattern exotropia, orthophoria in upgaze, 30 P.D. of exotropia in primary position, and 50 P.D. of exotropia in downgaze. Nystagmus was present with both eyes open, and the patient complained of oscillopsia in downgaze. Binocular visual acuity was 20/80. Ocular movement recordings done with scleral search coils disclosed a manifest latent nystagmus wave form in all fields of gaze except superiorly, where no nystagmus was detected with both eyes open (Fig. 5). After bilateral superior oblique tenotomies were performed, the patient had orthophoria by cover test and displayed only latent nystagmus. Binocular visual acuity was 20/25, and oscillopsia was denied. The postoperative ocular movement recordings show no nystagmus under binocular conditions, but latent nystagmus was present when covering either eye (Fig. 6).

Cases 4 and 5

Both patients were examined before they underwent previous surgical procedures and displayed manifest latent nystagmus wave forms. In Case 4, this 6-year-old patient, who had had previous surgery for infantile esotropia, had 20 P.D. of esotropia and 20 P.D. of left dissociated vertical deviation when first examined by us. After medial and superior rectus muscle recessions, the patient had orthophoria and binocular visual acuity improved one line.

The other 12-year-old patient (Case 5), who also had had previous surgery for infantile esotropia and dissociated vertical deviation, had 12 P.D. of right dissociated vertical deviation and 18 P.D. of left dissociated vertical deviation at the first examination with us. After bilateral inferior rectus muscle resections, the patient had orthophoria. Binocular visual acuity remained unchanged at 20/25. Postoperatively, both patients had only latent nystagmus.

Case 6

A 4-year-old girl simultaneously developed 25 P.D. of accommodative esotropia and nystagmus at 1 year of age. Monocular visual acuity was 20/70 in each eye. After correcting her hyperopia (R.E.: +4.00 +1.00 × 90 and L.E.: +4.00 +0.50 × 88), she had orthophoria,
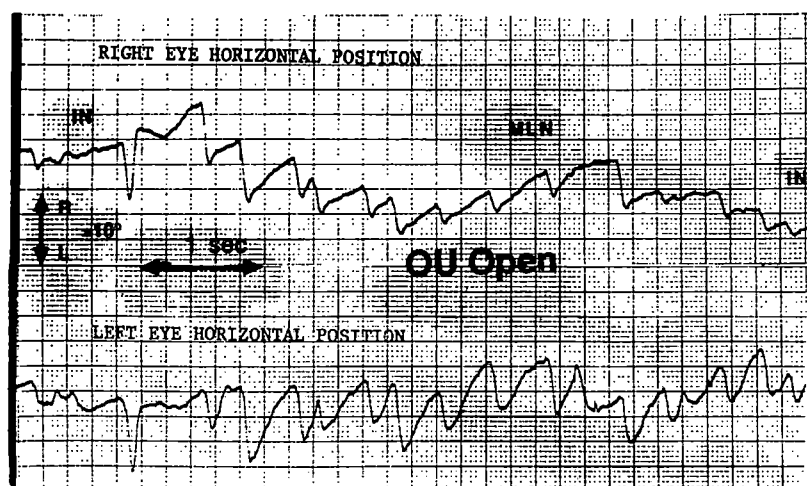
Fig. 1 (Zubcov and associates). Case 1. Preoperative ocular movement recordings (electro-oculography), binocular viewing.

only latent nystagmus, and showed improved binocular visual acuity of 20/40. She had a right head turn on initial use of spectacles that resolved in a short period of time.

Case 7

A 14-year-old girl had manifest latent nystagmus. After appropriate correction (R.E.: −7.25 +3.50 × 20 and L.E.: −2.25 +1.25 × 145) of the undercorrected myopia (R.E.: −4.25 +2.75 × 36 and L.E.: −4.50 +2.75 × 36), monocular visual acuity improved in the left eye from 20/200 to 20/60 and remained unchanged (20/60) in the right eye. The small esotropia (2 to 4 P.D.) and dissociated vertical deviation (4 P.D. in both eyes) remained unchanged. The manifest latent nystagmus, as noted by electro-oculography, decreased to 1 Hz and 0.5 degrees of amplitude without any change in binocular visual acuity. No foveation periods could be measured before or after treatment.

Case 8

A 12-year-old girl had nystagmus since the first day after birth. Binocular visual acuity in her preferred head position, right tilt of 10 to 15 degrees with chin up, was 20/50. Monocular visual acuity was R.E.: 20/200 and L.E.: 20/50.

The ocular movement recordings, done with torsional coils, showed a torsional nystagmus reduced upon right head tilt. In chin-up and chin-down position equally, the torsional movement decreased in reference to straight-ahead position. The horizontal electro-oculography disclosed manifest latent nystagmus at 2.5 Hz in primary position. The amplitude of the nystagmus was 8.3% of the cornea diameter as measured from the television tape. After appropriate correction (R.E.: −10.50 +2.00 × 20 and L.E.: −9.25 +1.50 × 115) of her undercorrected myopia (R.E.: −7.50 +1.50 × 58 and L.E.: −7.25 +1.25 × 116), visual acuity in the right eye improved to 20/80 and the nystagmus decreased to 1.5 Hz. The amplitude of the nystagmus measured in percentage of cornea diameter was 6.6%. Binocular visual acuity improved to 20/30.

Discussion

Electro-oculographic diagnostic criteria were used in this study for identification of patients with manifest latent nystagmus. These criteria established the correct diagnosis in four of the

Fig. 2 (Zubcov and associates). Case 1. Postoperative ocular movement recordings (electro-oculography), binocular viewing.
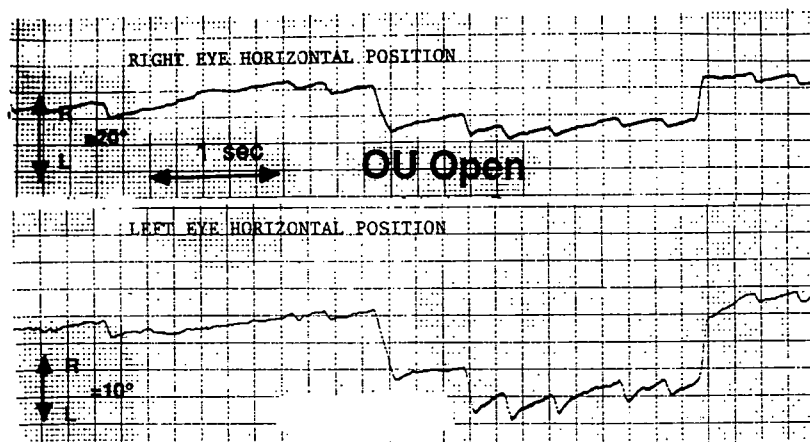
Fig. 3 (Zubcov and associates). Case 2. Preoperative ocular movement recordings (electro-oculography), binocular viewing.

eight patients (Cases 1 to 3 and 8) who were misidentified before the ocular movement recordings. Four of the eight patients showed a combination of wave forms: manifest latent nystagmus and infantile nystagmus in two patients (Cases 1 and 2), manifest latent nystagmus and high-frequency pendular nystagmus in one patient (Case 6), and manifest latent nystagmus with torsional nystagmus in one patient (Case 8). Dell'Osso, Schmidt, and Daroff[6] found that 54% of their 31 patients with manifest latent nystagmus demonstrated a combination of infantile nystagmus and manifest latent nystagmus wave forms. Recognition of these mixed types seems crucial in determining the optimal therapeutic approach and appropriate postoperative expectations of patients with nystagmus.

Observations of conversion of manifest latent nystagmus into latent nystagmus were made in 1952 and 1962 by Healy[12,13] who, by using an amblyoscope to move images onto the foveae of a patient with tropia, normal retinal correspondence, and nystagmus (clinically diagnosed manifest latent nystagmus), observed that the nystagmus stopped when alignment was achieved. Van Weerden and Houtman[5] reported one acquired case of strabismus with oscillopsia in a patient whose spontaneous nystagmus and oscillopsia disappeared after successful ocular muscle surgery. In an attempt to

elucidate the relationship between strabismus, manifest latent nystagmus, and latent nystagmus, Dell'Osso, Traccis, and Abel[1] described three patients, as documented by ocular movement recordings, who had no nystagmus during binocular viewing but latent nystagmus occurred when covering either eye. When the eyes assumed a tropic position, however, manifest latent nystagmus was present.

We found that in the five patients who underwent successful strabismus surgery and in the one patient whose eyes were aligned through optical correction, manifest latent nystagmus was converted to latent nystagmus. We believe that the equal visual input on corresponding retinal loci the eyes receive when aligned is the cause of the conversion. Orthophoria by itself or a change in fusional status alone are not responsible for the conversion.[4]

Dell'Osso, Traccis, and Abel[1] and van Weerden and Houtman[5] did not report the visual acuity of their patients when they were in the manifest latent nystagmus stage vs the latent nystagmus stage. In our study, four of five patients (Cases 1 to 4) with manifest latent nystagmus underwent successful strabismus surgery, subsequently demonstrated conversion of the manifest latent nystagmus into latent nystagmus, and showed improvement of binocular visual acuity (Figs. 1 to 6, Table). Also binocular visual acuities of two of the
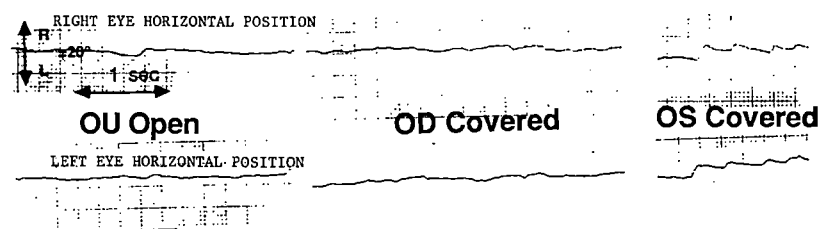
Fig. 4 (Zubcov and associates). Case 2. Postoperative ocular movement recordings (electro-oculography); binocular viewing, right eye covered, and left eye covered.
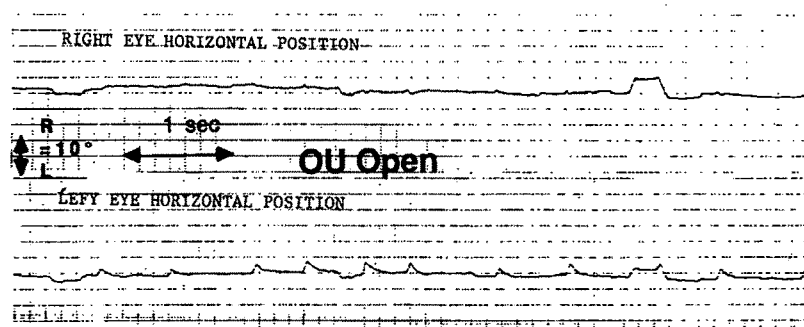
Fig. 5 (Zubcov and associates). Case 3. Preoperative ocular movement recordings (magnetic scleral eye coil), binocular viewing.

three patients who had optical treatment improved after the conversion of manifest latent nystagmus to latent nystagmus (Case 6) or after reduction of manifest latent nystagmus (Case 8).

In Case 1 visual acuity was measured by sweep visual-evoked potential, with which we have had extensive experience for infants with various visual disorders. Our sweep visual-evoked potential visual acuity estimates have correlated well with optotype visual acuity; thus we have confidence that the modest increase in visual acuity of this patient is real.[9] This could be explained by the pendular nystagmus wave form with longer foveation time that replaced the manifest latent nystagmus. Case 2 had no nystagmus in primary position since the null point of the infantile nystagmus was therapeutically moved and the manifest latent nystagmus disappeared after the correction of the tropia. The Kestenbaum procedure is thought to improve patients' visual acuities.[14] The less than one line improvement in this patient is probably because of the conversion of manifest latent nystagmus to latent nystagmus, as well as the result of a Kestenbaum procedure. Our findings are best demonstrated in Case 3. In this patient the complete disappearance of nystagmus when viewing binocularly can account for improved visual acuity. Two patients (Cases 4 and 5) entered the study after already undergoing one surgical procedure; therefore, we could not document their nystagmus before the first treatment but only between that one and subse-

quent treatments. Both of these patients now have orthophoria, and the manifest latent nystagmus has converted to latent nystagmus. In Case 4, the patient has one Snellen line increase in binocular visual acuity (Table). This modest increase in a 6-year-old child might be the result of a learning effect rather than true visual acuity improvement.

One patient (Case 6) showed improved binocular visual acuity after correction of the accommodative esotropia with spectacles. Improved visual acuity might have been caused by the conversion of manifest latent nystagmus to latent nystagmus. The correction of the hyperopic astigmatism may have contributed to the improvement of binocular visual acuity by improving the monocular visual acuity. In Case 8, monocular visual acuity improved after appropriate correction of the myopia. The manifest latent nystagmus also dampened. This suggests a close relationship between the level of visual acuity and the intensity of manifest latent nystagmus. We speculate as to whether visual acuity improvement makes the nystagmus better or vice versa. The better the monocular visual acuity of the fixing eye, the lower the manifest latent nystagmus intensity, as demonstrated in this patient. One of us (R.D.R.) has observed a conversion of manifest latent nystagmus to latent nystagmus while treating amblyopia in patients with manifest latent nystagmus. The lack of binocular improvement demonstrated in Case 7 seems to support the hypothesis that a decreasing amplitude of manifest latent nystag-
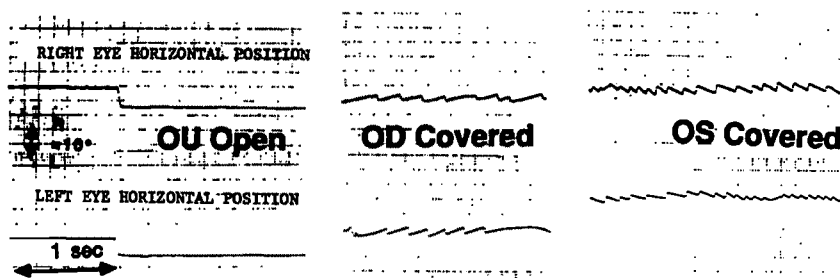
Fig. 6 (Zubcov and associates). Case 3. Postoperative ocular movement recordings (magnetic scleral eye coil); binocular viewing, right eye covered, and left eye covered.

mus will not improve visual acuity.[3] Conversely, the improvement in binocular visual acuity with reduction of the manifest latent nystagmus in Case 8 is similar to the findings of Evans, Biglan, and Troost,[2] who documented by simultaneous, quantitative ocular movement recordings and 16-mm movies that the latent nystagmus was least intense during the best recorded visual acuity of seven subjects.

In Case 8 the patient had orthophoria and both manifest latent nystagmus and torsional nystagmus (infantile nystagmus) with a right head tilt of 10 to 15 degrees with the chin up. The early occurrence suggested infantile nystagmus. Subsequent wave form analysis, however, disclosed a typical manifest latent nystagmus, jerk nystagmus, along with an additional torsional component. This patient does not have tropia along with the manifest latent nystagmus. Lang[15] reported that only two of 198 patients with latent nystagmus had no strabismus. Dell'Osso, Traccis, and Abel[1] considered strabismus (phoria or tropia) a necessary but insufficient cause of manifest latent nystagmus or latent nystagmus. Possibly in Case 8 the patient had a small-angle tropia that was not detected because of the high-amplitude latent nystagmus.

Four of our five patients who had operations for esotropia had symmetric surgery. The manifest latent nystagmus lessened whenever alignment of the eyes was achieved. Ishikawa[16] performed a recess-resect surgical procedure on his five esotropic patients which, he believed, gave better results with regard to the intensity of nystagmus and visual function. There are no data in his study, however, to substantiate this claim. Metz and Smith[17] described one patient who underwent symmetric surgery with good postoperative results with regard to the nystagmus intensity. Whether symmetric or asymmetric surgery is the better approach in patients with manifest latent nystagmus is debatable.

The improvement in visual acuity obtained in two of our eight patients (Cases 3 and 4) points to the manifest latent nystagmus conversion as a cause. In four of the patients (Cases 1, 2, 6, and 8) other plausible explanations may be the cause of our reported improvement such as newer, less proven techniques of assessing visual acuity, simultaneous surgical procedures, optical corrections, or learning effects. Ocular muscle surgery in patients with manifest latent nystagmus seems to have not only a cosmetic effect, but it also converts manifest latent nystagmus into latent nystagmus.

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The Fixed and Dilated Pupils of Premature Neonates

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We examined on a weekly basis the pupils of 30 preterm infants. In relative darkness (< 10 foot-candles [ft.-c.] of illumination), the pupils measured a mean of 4.7 mm in the youngest infants (26 weeks' postconceptional age) when the corneal diameter was 7.0 mm. The pupils became progressively smaller, reaching 3.4 mm at 29 weeks' postconceptional age (P < .001). The pupils did not constrict to the stimulating light (600 ft.-c.) until a mean of 30.6 weeks' (± 1 week) postconceptional age. Mydriasis should not be considered indicative of a central nervous system disorder, and a pupil unresponsive to light should not be considered suggestive of blindness until a preterm infant reaches at least 32 weeks' postconceptional age.

In a previous study, we characterized the pupil diameter in relative darkness and after stimulation by light of 100 newborns.[1] We found that the mean pupil diameter in relative darkness was about 3.5 mm and was independent of postconceptional age. Conversely, the amount of pupil constriction to light was directly proportional to postconceptional age. However, the data for the few premature infants (< 31 weeks' postconceptional age) studied were inconsistent. Most of these infants did not respond to light, but a few did. To characterize the pupils of preterm neonates more properly, we studied a cohort of premature newborns on a weekly basis. We compared the pupil diameter in relative darkness and the light response in the preterm infants as they mature.

Subjects and Methods

Thirty newborn infants of less than 31 weeks' postconceptional age were entered into the study. Postconceptional age is defined as the gestational age at birth as determined by the Dubowitz classification plus the number of weeks since birth.[2] No neonate was included in the study if any ocular abnormality was detected at the time of examination or thereafter, including retinopathy of prematurity. Newborns with any systemic abnormality such as sepsis, hydrocephalus, or a history of maternal or fetal drug intoxication were also excluded. All infants underwent cerebral ultrasonography and were excluded if intraventricular hemorrhage was noted. Many of these premature neonates were intubated for respiratory distress.

An effort was made to measure initially the pupil diameter in the darkest environment that would permit observation. If the nursery was too bright, a black drape was placed around the incubator to darken the environment. In all cases, the area of the newborn's face was exposed to less than 10 foot-candles (ft.-c., 110 lux) as measured with a light meter using a flat plane diffuser. The pupil diameter was measured with a millimeter ruler or a hemispherical pupil ruler. Light calibrated to precisely 600 ft.-c. (6,400 lux) was directed into the pupil at the testing distance with the same light meter, and the pupil diameter measurement was repeated. Additionally, the corneal diameter was determined. All measurements were made simultaneously by at least two of us. The determination was not recorded until all of the examiners agreed. The examination was repeated weekly until the pupils demonstrated a response to light of at least 0.5 mm.

Results

The 30 neonates were initially examined at a mean of 7.8 days (± 7.1) after birth and at 28 (±

1.5) weeks' postconceptional age (range, 25 to 30 weeks). Of these, 17 neonates were initially examined at a postconceptional age of less than 29 weeks. The mean birthweight was 920 g (± 233 g) (range, 550 to 1,330 g).

In relative darkness, the mean pupil diameter was 3.9 mm (± 0.9 mm) at the initial examination. At that examination, the cornea had a mean diameter of 7.5 mm (± 0.6 mm). Figure 1 shows the relationship between postconceptional age and the pupil diameter in relative darkness. By t-test, the difference in the pupil diameter in relative darkness between 26 and 31 weeks (4.7 mm ± 0.3 mm and 3.4 mm ± 0.5 mm, respectively) was significant (P < .001). The correlation coefficient between the pupil diameter in darkness and postconceptional age was −0.45 (P < .001). Between 26 and 31 weeks' postconceptional age, regression analysis yielded the following relationship: pupil diameter in relative darkness = 10.0 − 0.22 A, with A representing the postconceptional age in weeks. The standard error of the estimate was 0.69.

No pupil demonstrated a response to light at the initial examination. The mean postconceptional age at which a light response of at least 0.5 mm was evident was 30.6 weeks (± 1.0) with a range of 28 to 32 weeks (Fig. 2). At that point, the mean pupil diameter in relative darkness was 3.4 mm (± 0.6 mm).

Discussion

Earlier in this century, European authors investigated the pupil response to light in prema-
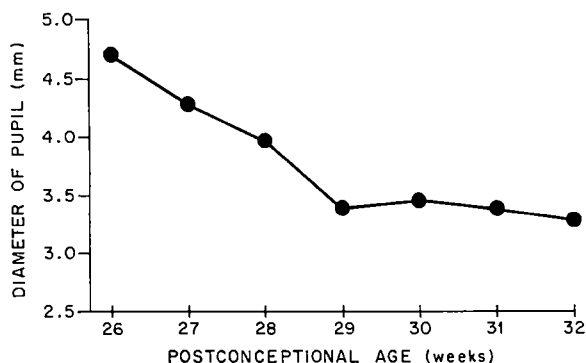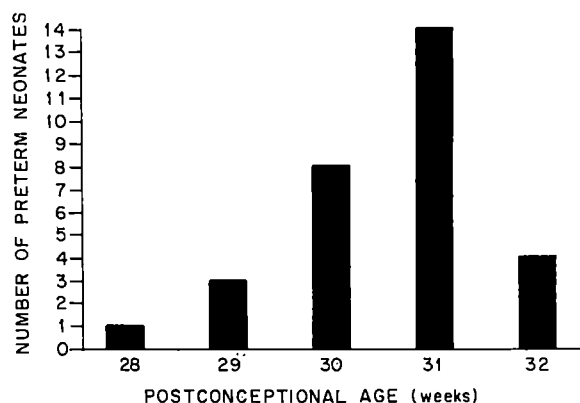
Fig. 2 (Isenberg, Molarte, and Vazquez). The postconceptional age at which the pupils first responded to light (600 ft.-c.).

ture infants. At that time, however, there were no instruments available to measure and control the light levels of the environment and the stimulating light source. Additionally, at that time no proper study had established criteria for evaluating the postconceptional age.[2] Minkowski[3] found no pupil light response in newborns up to 7 months' gestational age. In four infants examined before 6 months' gestational age, Magitot[4] found no response to light, mentioned that the pupils were dilated, but did not provide any data. More recently, using a penlight as the stimulating light source in seven infants under 29 weeks' gestational age, Robinson[5] found a light response to be usually absent. In four babies followed up serially, he reported the light response to appear between 30 and 31 weeks' gestational age.

In relative darkness, this study showed that neonates at a postconceptional age of 26 weeks had a mean pupil diameter of 4.7 mm. This may not seem mydriatic to physicians accustomed to examining adults. It should be realized, however, that at that age the mean corneal diameter was found to be only 7.0 mm. For comparison, the pupil of an infant at 26 weeks' postconception would have a relative diameter of 7.9 mm in the adult eye with a corneal diameter of 11.7 mm.[6] This would decrease in diameter to an adult equivalent of 5.3 mm by 29 weeks after conception. Our previous study found older preterm neonates to have a mean pupil diameter of about 3.5 mm in relative darkness, which was unrelated to the postconceptional age. The current investigation indicates that the diameter of 3.5 mm is reached at 29 weeks and then remains at that level.

Fig. 1 (Isenberg, Molarte, and Vazquez). The diameter of the pupil in relative darkness (< 10 ft.-c.) in preterm neonates.

The cause of the dilated pupil in preterm neonates is unknown. One possible explanation is increased sympathetic activity or decreased parasympathetic tone to the musculature of the iris, or both. Preterm babies, however, have demonstrated little or no mydriatic responses to tyramine and hydroxyamphetamine hydrobromide eyedrops because the synthesis, storage, or release of noradrenaline is deficient in smaller babies.[7,8]

A more tenable explanation may be found in the embryology literature. The sphincter muscle of the pupil first appears in the fourth month of gestation from neuroectodermal tissue. In the sixth month, mesodermal elements are recognized in the sphincter muscle in the form of connective tissue septa containing capillaries, which develop further into the seventh month.[9] Ruprecht and Wulle[10] found electron microscopic changes occurring in the sphincter muscle as late as the seventh month, which consisted of the development of intermediate and tight cell junctions. Despite the observation that the sphincter pupillae muscle is histologically complete by the eighth month, Mann[11] speculated that a direct reaction to light was possible as early as the fourth month of gestation. Our study indicates that this hypothesis was incorrect. Mann also observed in a postmortem series that the pupil diameter increases from early fetal life until the fifth month and then barely changes. Although our in vivo study showed the pupil diameter in relative darkness to decrease between the 26th and 31st week, the diameter reached and maintained at that time was about 3.5 mm, similar to that reported by Mann.

The dilator pupillae muscle first appears in the sixth month of gestation, much later than the sphincter muscle. Since the dilator does not become vascularized or have any mesodermal septa,[11] it may achieve maturation before the sphincter. Thus, the mydriatic effect of the dilator may precede the miotic effect of the sphincter producing a net mydriasis in the preterm newborn.

We found that the light response begins at a mean of 30.6 weeks' postconceptional age. That response was usually the minimally accepted miosis of 0.5 mm, since we believed that that was the minimal response that could be definitely appreciated by both examiners. However, the light response was noted to increase in subsequent weeks. By 33 weeks' postconcep-

tional age, the mean pupil constriction to light was 1.5 mm. This is similar to our previous study, which found a net miosis of 1.2 mm at that age.[1]

A possible factor contributing to the absence of pupil response to light in preterm infants might be anatomic changes occurring in the iris. Purtscher[12] has reported that the anterior leaf of the iris stroma undergoes regression in the human baby, unlike dogs or monkeys. The presence of this fibrous layer in the preterm infant may mechanically inhibit constriction of the pupil to light stimulation. Another explanation for the development of the light response would be maturation of the Edinger-Westphal nucleus, or its connections to the iris sphincter, or both.

The presence of fixed and dilated pupils in preterm infants may be valuable to neonatologists as well as ophthalmologists. In the past, the finding of a mydriatic pupil in a neonate suggested to neonatologists to rule out perinatal asphyxia or massive intraventricular hemorrhage.[13] However, our study suggests that mydriasis is normal in preterm infants. Additionally, the finding of a pupil unresponsive to light in a preterm infant might mislead the physician to believe that the eye is blind. Examination based on pupil findings should be delayed until about 32 weeks' postconceptional age when the pupil is no longer physiologically mydriatic and has begun to demonstrate a pupil response to light.

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OPHTHALMIC MINIATURE

His eyelids, docile now, fell over his corneas in the same natural way with which his arms and legs mingled in a gathering of members that were slowly losing their independence, as if the whole organism had turned into one single, large, total organism, and he—the man—had abandoned his mortal roots so as to penetrate other, deeper and firmer, roots: the eternal roots of an integral and definitive dream.

Gabriel García Márquez, Collected Stories
New York, Harper & Row, 1984, p. 15

An Optical Model to Describe Image Contrast With Bifocal Intraocular Lenses

Neal H. Atebara, B.S., and David Miller, M.D.

We attempted to quantify the decrease in contrast associated with the concentric-style bifocal intraocular lens by using a model eye and bifocal intraocular lens, with a model unifocal intraocular lens as a control. When imaging near objects, pupils smaller than 2.5 mm produced image contrast of 100% of the control; larger pupils degraded contrast to 25% for a 6-mm pupil. For distant objects, pupils smaller than 2.5 mm produced image contrast of 70% to 95% because of the pinhole effect; larger pupils engaged the distance portion of the intraocular lens and maintain 80% contrast on average. Thus, the bifocal intraocular lens produced image contrast greater than 70% in all situations tested, except when imaging near objects with a pupil larger than 3.5 mm. The data suggest that image contrast is highly dependent on pupil size and object distance.

BIFOCAL INTRAOCULAR LENSES attempt to give the patient clear vision at reading distance and at far distance, in contrast to standard unifocal intraocular lenses that only focus on distant objects. The goal is to free the patient with pseudophakia from ever needing spectacles.

Bifocal intraocular lenses have several potential problems. First, concentric-type bifocal designs with central add lenses are sensitive to decentration within the pupillary aperture. Second, the calculations for distance power and for add lens power must be exact, otherwise the patient will require corrective spectacles. Third, these lenses are associated with a decrease in image contrast.[1] We attempted to quantify this last problem.

Retinal image contrast is determined primarily by the intraocular lens' ability to focus light on the retina. Bifocal intraocular lenses consist effectively of two lenses: the distance power to bring distant objects into focus, and the higher-powered add lens to bring near objects into focus. This configuration precludes the bifocal intraocular lens from bringing all light from an object into simultaneous focus on the retina. To view distant objects, the base intraocular lens brings the image into focus; the add lens, however, in effect steals some of the light that would have been focused and spreads defocused light onto the retina, which decreases image contrast (Fig. 1, bottom). Conversely, the add lens brings objects at reading distance into focus while the distance portion of the lens scatters light and lowers contrast (Fig. 1, top).

Pupil size also markedly affects image contrast in eyes with bifocal intraocular lenses. Pupil size determines the ratio of add lens to distance lens that lies in the pupil. Larger pupils allow more distance lens to refract incoming light, which assists the imaging of distant objects and impedes the imaging of near objects. Pupils smaller than the add lens actually restrict the bifocal intraocular lens to function essentially as a high-diopter unifocal lens (Fig. 2).

We attempted to quantify the effects of bifocality and pupil size on image contrast by using an optical model of the human eye. As an example of current bifocal intraocular lens designs, we used the concentric-type configuration, which consists of a base distance-power lens with a concentric add lens 2.0 mm in diameter and approximately 3.0 diopters in power (Fig. 2).

Material and Methods

We constructed a system approximating the optics of the human eye based on the measurements of the human eye made by Gullstrand[2]
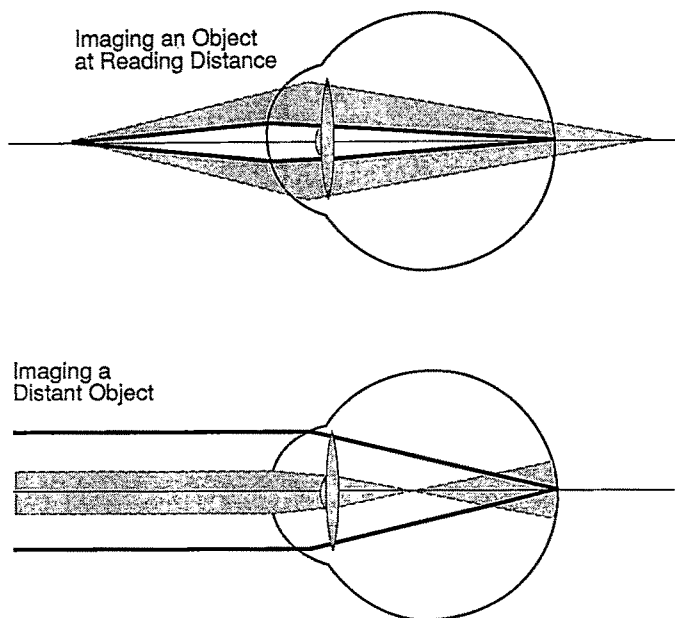
Fig. 1 (Atebara and Miller). Simplified ray tracing of the human eye with a bifocal intraocular lens implant. Top, The add lens brings the image of a near object into focus on the retina (solid line), but the distance portion of the lens scatters defocused light (shaded region). Bottom, The distance lens brings the image of a distant object into focus (solid line), and the add lens scatters light (shaded region).

and confirmed by modern ultrasonic measurements.[3,4] To facilitate manipulation of the optical elements, the model eye was built 4.5 times larger than the human eye. The distances between the optical elements (for example, the distance from the cornea to pupil) and their
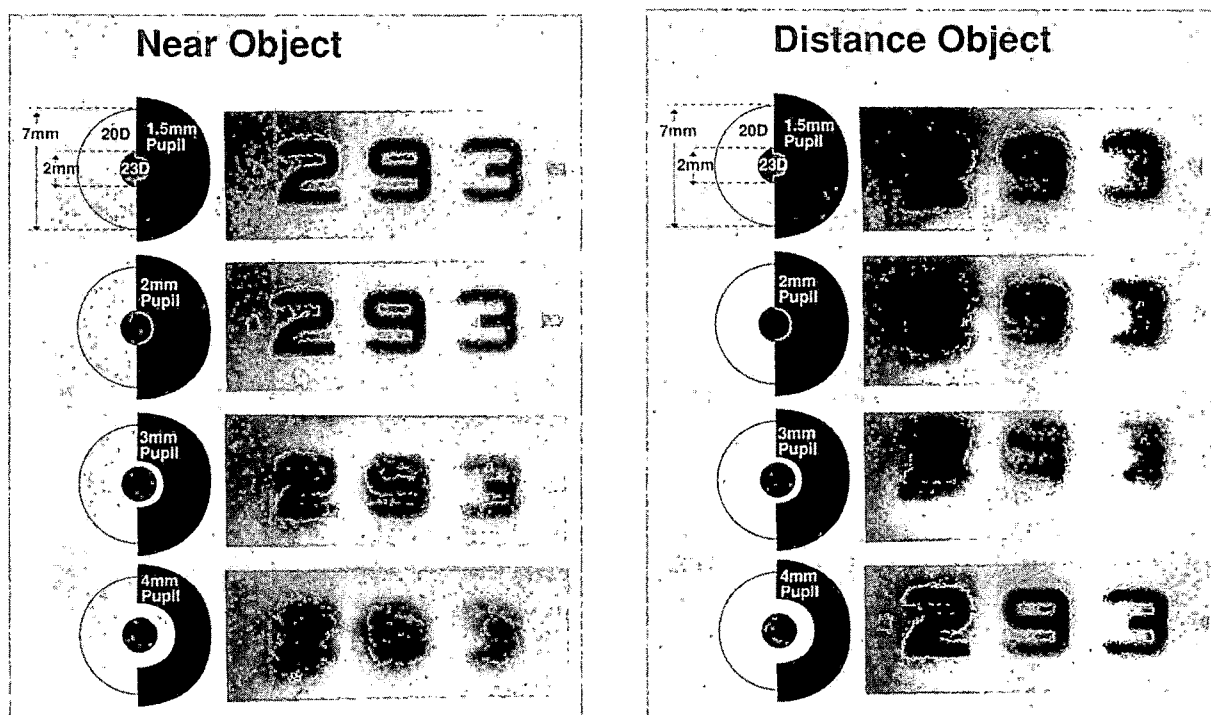
Fig. 2 (Atebara and Miller). Photographs of 20/45-equivalent Snellen letters produced by the model eye with simulated bifocal intraocular lens. Diagrams of pupil size relative to the bifocal intraocular lens are shown. Left, Images from a reading-distance object. Right, Images from a distant object. Because of the effects of magnification and changes in contrast caused by photographic and printing processes, the overall blur is greatly exaggerated. However, because the f-number of the model eye is kept constant with that of the human eye, the relative effects of pupil size on image contrast can still be appreciated.

dimensions (for example, pupil diameter) were likewise scaled up by a factor of 4.5. Also, to accommodate the larger dimensions, the dioptric powers of the optical elements were scaled down to 1/4.5 of the actual powers of the human eye (for example, a +4.5-D lens was used to simulate a +20-D intraocular lens). The f-number of the optical system, the distance of the image from the aperture divided by the diameter of the aperture, remained identical to that of the human eye. The image contrast produced should not be altered significantly by this optical system of larger physical dimensions. A schematic of the model human eye is shown in Figure 3.

It should also be noted that the optical elements of the model system were entirely in air, unlike the human eye where the crystalline lens and the endothelial surface of the cornea are immersed in aqueous humor. The dioptric powers of the model optical elements, however, were based on cornea and crystalline lens refractive powers in their physiologic environment. Thus, this discrepancy did not significantly alter image contrast.

The model bifocal intraocular lens was constructed by using a biconvex trial lens that was +4.5 D in power and 31.0 mm in diameter (in our model system this was proportional to a +20-D distance power intraocular lens, 7.0 mm in diameter). A hard contact lens +0.68 D in power and 8.9 mm in diameter was affixed to the center of the front surface of the trial lens to simulate the add portion of the intraocular lens (this was proportional to a +3-D add lens, 2.0

mm in diameter). A model unifocal intraocular lens consisting of a +4.5-D trial lens, 31.0 mm in diameter, without the add power, served as a control (this was proportional to a +20-D unifocal intraocular lens, 7.0 mm in diameter).

The model cornea was a trial lens +9.7 D in power placed 24.0 mm in front of the model bifocal intraocular lens (proportional to a +43 - D cornea with a distance of 5.4 mm from corneal endothelium to the center of the crystalline lens). The model pupil was a variable aperture with diameters ranging from 6.7 to 31.1 mm, placed 16.4 mm behind the model cornea (representing a pupillary range of 1.5 to 7.0 mm and a distance of 3.7 mm between the corneal endothelium and iris).

An illuminated projector slide of Snellen letters 22.5 mm in height was positioned in front of the model eye and represented the patient's visual world. The Snellen letters were positioned 155 cm in front of the model eye to simulate a reading distance of 35 mm and a Snellen visual acuity equivalent of 20/45 (Fig. 3, top). A +0.7-D biconvex trial lens placed at its focal length (145 cm) from the Snellen letters projected parallel light rays into the model eye, which simulated a distant object (Fig. 3, bottom).

The model retina was a polished white screen. The projected image was 1.3 mm in height (corresponding to a 0.3-mm retinal image in the human eye). The image was photographed with a camera fixed to an operating microscope.

In the experiment, the Snellen letters were
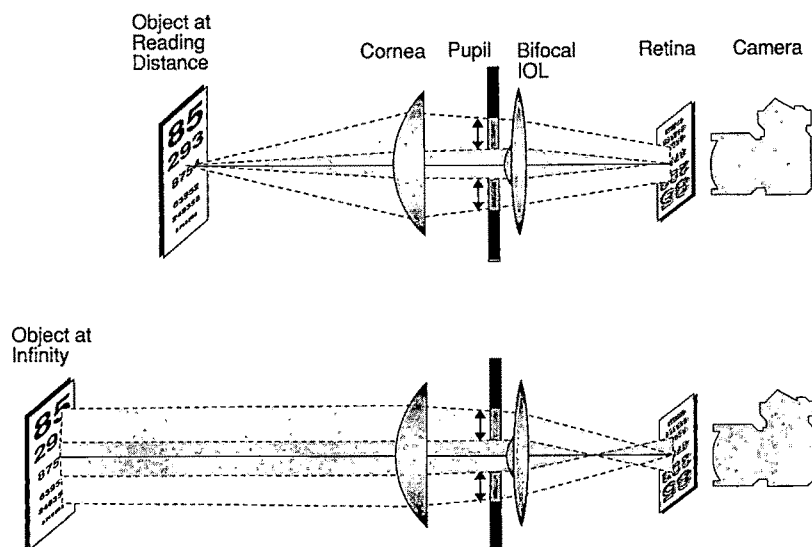
Fig. 3 (Atebara and Miller). The model human eye used in the experiments. The Snellen letters are positioned at near (top) and far (bottom) distances from the optical system.

first positioned at a far distance, and the image was focused onto the retinal screen. With the model bifocal intraocular lens in place, pupil size was varied from 1.5 to 7.0 mm (model aperture diameters of 6.7 to 31.1 mm), and each image was photographed to give a qualitative idea of how image contrast was affected by pupil size. The Snellen letters were then positioned at a near distance, and the experiment was repeated.

Quantitative data on image contrast were obtained by measuring object illumination (I_0) and background illumination (I_B) of the Snellen letter images by using a digital photometer. Illumination at the point of the intersection of the number "9" was used for I_0, and the point midway from the number "9" to the adjacent number "3" was used for I_B. Contrast was calculated by using the equation $(I_B - I_0)/(I_B + I_0)$. Control experiments replaced the bifocal intraocular lens with a +20-D unifocal lens (model trial lens was ÷4.5 D) for the far control and a +23-D unifocal lens (model trial lens was +5.2 diopters) for the near control.

Results

Figure 2 represents the images produced by the model eye with the concentric-type bifocal intraocular lens. In Figure 2, left, the model eye is imaging a near object with pupil sizes of 1.5, 2.0, 3.0, and 4.0 mm, respectively (model aperture sizes of 6.7, 8.9, 13.3, and 17.8 mm, respectively). These photographs are intended merely to illustrate relative changes in image contrast with different pupil sizes. These images are greatly magnified and therefore display a much higher degree of apparent blur than the images seen at their actual size on the retina. Further, photographic and printing processes affect the overall contrast.

At 1.5 and 2.0 mm (model aperture sizes of 6.7 and 8.9 mm, respectively), the pupil was smaller than or equal to the add lens, and light entered only through the central add lens. Thus, the add lens alone produced high-contrast images of the near object. As the pupil dilated beyond 2.0 mm (model aperture sizes larger than 8.9 mm), light also entered through the distance portion of the lens, which spread unfocused light onto the screen and decreased the contrast. Pupillary dilation to 4.0 mm (model aperture size of 17.8 mm) exposed even more distance lens, which further decreased contrast.

The unfocused image was not exactly centered on the focused image, which produced a shadow. This indicated that the various elements of the optical system were not centered precisely, a technical problem we could not correct fully. In our photometric measurements, the area of overlap of the two images was used to approximate the illumination from centered images. This technical problem of monocular diplopia did not seem to be a problem clinically with the manufactured intraocular lenses currently in use.

In Figure 2, right, the model eye is imaging a distance object. With the pupil constricted to 1.5 mm (model aperture size of 6.7 mm), only the near-imaging add lens was engaged in imaging the distant object. Oddly enough, the contrast was still relatively high. The 1.5-mm pupil (model aperture size of 6.7 mm) was acting as a pinhole, bringing the distant object into focus even though the add lens can ordinarily image only near objects.[5] As the pupil dilated to 2.0 mm (model aperture size of 8.9 mm), some of the pinhole effect was lost, and image contrast fell. At 3.0 mm (model aperture size of 13.3 mm), the pinhole effect was minimal and the add lens only served to lessen image contrast of the distant object. At 4.0 mm (model aperture size of 17.8 mm), the image formed by the distance portion of the lens overwhelmed that from the add lens, and a high-contrast image was produced once again.

Figure 4, left, is a graph of image contrast vs pupil size in the model eye that is imaging a near object. The control line (dashed) represents the image contrast when a +23-D unifocal lens (model trial lens of +5.2 D) replaces the model bifocal intraocular lens. As expected, pupil size did not significantly affect image contrast with the unifocal lens.

With the bifocal intraocular lens, however, image contrast was affected markedly by pupil size. When imaging a near object, the central add lens produced the dominant image. At pupil diameters equal to or less than the add diameter of 2.5 mm (model add diameter is 11.2 mm), the contrast produced by the add lens was high, equal to the control. As the pupil dilated beyond the add lens, the distance portion of the lens produced defocused light, which caused a decrease in contrast. Contrast declined precipitously as more of the distance lens was exposed, dropping to 25% of the control with a pupil that is 6.0 mm (model aperture diameter of 27.0 mm). Pupil sizes larger than 7.0 mm (model

Near Object

Far Object
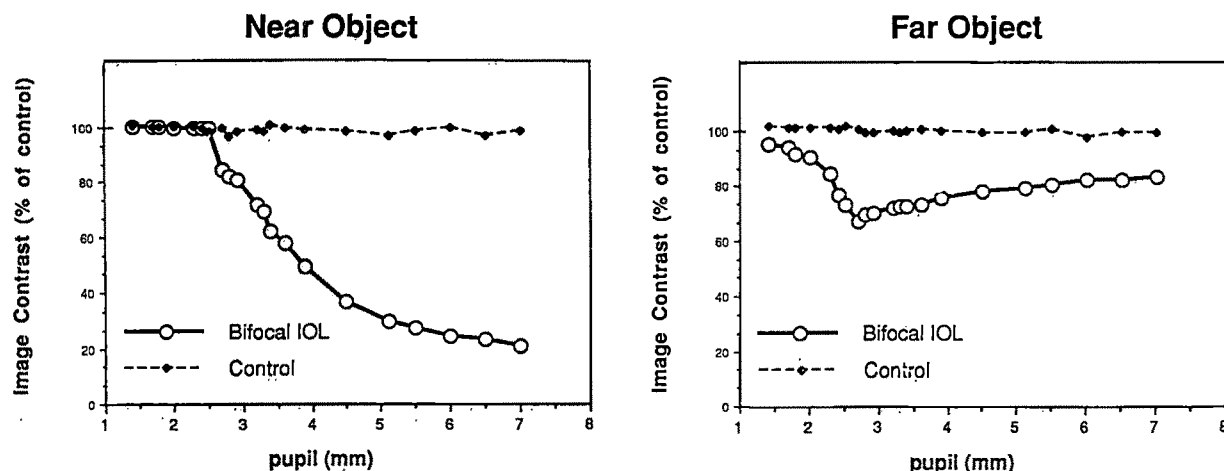
Fig. 4 (Atebara and Miller). Plot of image contrast at various pupil sizes produced by the model eye. The image contrast produced by the bifocal intraocular lens is plotted in a solid line, and the control is plotted in a dashed line. The Snellen letters are positioned at a near (left) and far (right) distance.

aperture sizes larger than 31.0 mm) were not studied because of instrument limitations.

Figure 4, right, is a graph of the performance of the bifocal intraocular lens when imaging distant objects. With pupil diameters less than 2.0 mm (model aperture diameters less than 8.9 mm), only the add lens was exposed to incoming light rays. A resultant image with low contrast might be expected; however, the image contrast measured between 90% and 95% of the control. The pinhole effect of the small pupil accounted for this finding. With pupil diameters between 2.0 and 2.5 mm (model aperture diameters between 8.9 and 11.2 mm, respectively), contrast decreased as the pinhole effect weakened and as the distance lens became increasingly exposed, which contributed unfocused light onto the retinal screen. At 2.5 mm (model aperture diameter of 11.2 mm), image contrast hit a minimum of 70% of the control. With pupil sizes larger than 2.5 mm, enough distance lens became exposed to produce an increase in image contrast, with a plateau at approximately 80% of the control. Contrast measurements never reached that of the control because of the light scattered by the add lens.

Discussion

The data confirm that image contrast produced by the bifocal intraocular lens is highly dependent on pupil size and object distance. For reading-distance objects (Fig. 2, left, and

Fig. 4, left), image contrast is maximal with pupil diameters less than 2.5 mm (model aperture diameter of less than 11.2 mm), with contrast at 100% of the control. With larger pupils, image contrast falls rapidly, dropping to 25% of the control for a pupil that is 6.0 mm (model aperture diameter of 27.0 mm). For far objects (Fig. 2, right, and Fig. 4, right), the best image contrasts of 90% to 95% of the control are generated with pupil sizes less than 2.0 mm (model aperture diameter of less than 8.9 mm) because of the pinhole effect. At 2.5 mm (model aperture diameter of 11.2 mm), image contrast reaches a minimum of 70% because the enlarging pupil weakens the pinhole effect, while at the same time little distance lens is engaged. At pupil sizes larger than 3 mm (model aperture diameter of 13.3 mm), enough distance lens is exposed to produce relatively high-contrast images at approximately 80% of the control. Thus the bifocal intraocular lens produces good image contrast of at least 70% in all circumstances except when imaging a near object with a pupil larger than 3.5 mm (analogous to the patient reading a book in a dimly lit room).

Despite the low image contrast produced by the bifocal intraocular lens in some situations, patients who use the concentric-type bifocal intraocular lens have, in general, been satisfied. There are several possible explanations for this. The answer most likely lies in the contrast enhancement of the retinal image by the neuro-circuitry of the retina and visual cortices. That is, the retina and brain are able to take relatively low-contrast retinal images and enhance the information they contain for better recognition.

Also, pupillary size in elderly recipients of bifocal intraocular lenses may have been small, and they may have benefited from a large depth of focus (pinhole effect). Finally, contrast sensitivity has been shown to decrease with age,[6] and it is possible that elderly implant recipients may be less sensitive to the decline in contrast produced by the bifocal intraocular lens.

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OPHTHALMIC MINIATURE

"Are yours for long sight or short sight?" asked Mrs. Brandon. "Astigmatism," said Mr. Grant. "I squint with one eye and not with the other, or something of the sort. My man says I'll get over it if I wear glasses for a few years."

"Mine are for short sight," said Mrs. Brandon proudly. "I can see anything, absolutely anything at a distance, but close to my eyes are quite useless to me."

Mr. Grant found the thought of Mrs. Brandon's blue eyes, endowed with the eagle's sight for ranging over the great free distances but betraying their owner for the level of every day's most quiet needs, so moving that he sat silent.

Angela Thirkell, *The Brandons*
London, The Hogarth Press, 1988, p. 105

Ab Interno Laser Sclerostomy in Aphakic Patients With Glaucoma and Chronic Inflammation

Richard P. Wilson, M.D., and Jonathan C. Javitt, M.D.

Five patients with aphakia, glaucoma, and chronic inflammation were treated with ab interno sclerostomy by using the continuous wave Nd:YAG laser focused through a sapphire probe. After a follow-up period of 24 to 28 months, three of five patients had good intraocular pressure control. The sclerostomy failed in one patient when it was occluded by vitreous. The second failure was attributed to closure of the sclerostomy because of chronic intraocular inflammation.

SEVERAL GROUPS OF INVESTIGATORS have developed techniques of filtering surgery using an ab interno approach to eliminate the usual conjunctival dissection. Brown and associates[1] have developed a mechanical trephine (trabecuphine) that can be directed across the anterior chamber to produce a sclerectomy. March and associates[2,3] investigated a conventional Q-switched Nd:YAG laser to produce a laser sclerostomy. Jaffe and associates[4] and Gaasterland and associates[5] described successful ab interno laser sclerostomy in primates with an argon laser and a fiberoptic delivery system.

The fiberoptic delivery system can be enhanced by the addition of a sapphire tip, which focuses the laser energy and provides maximum energy density at the tissue interface while minimizing backscatter of energy to surrounding tissue.[6,7] The continuous wave Nd:YAG laser energy provides both cutting and coagulating properties when directed through a sapphire crystal.

Javitt and associates[8,9] previously reported the initial series of experiments using this system in rabbits. Higginbotham, Kao, and Pey-

man[10] reported that ab interno sclerostomy using the continuous wave Nd:YAG laser in rabbits resulted in longer duration of filtration than did traditional filtering surgery. In the present study, we examined initial results with laser sclerostomy ab interno in humans.

Patients and Methods

The patients selected for study had aphakia, uncontrolled glaucoma, chronic uveitis, and severe scarring of the superior portion of the bulbar conjunctiva. All patients gave informed consent. The consent form and clinical protocol were approved by the investigational review board of the Wills Eye Hospital, Thomas Jefferson University.

For retrobulbar anesthesia, patients were injected with 3 ml of a 1:1 mixture of 2.0% mepivacaine hydrochloride and 0.75% bupivacaine hydrochloride. After the preoperative preparation, the patient was draped in a sterile fashion and positioned under the operating microscope. A conjunctival bleb was raised in the inferonasal quadrant by injecting 0.5 ml of balanced salt solution or hyaluronate sodium into the subconjunctival space.

A 1.5-mm incision was then made in the superotemporal limbus. A vitrectomy was performed in three patients (Cases 2, 3, and 5) with a standard cutting/aspiration instrument. One patient (Case 4) had had a previous vitrectomy. Hyaluronic acid was instilled into the anterior chamber. A 1-mm diameter sapphire laser scalpel with tip diameter of 200 μm was introduced through the limbal incision. With the aid of a Barkan lens in the first two patients (Cases 1 and 2) and by direct visualization in the remaining three patients (Cases 3 through 5), the sapphire tip was placed in contact with the sclera in the region of Schwalbe's line (Figs. 1 through 5).

Between three and five pulses of 800 mJ (8 W × 0.1 second), or one to two pulses of 2.4 J (12

Fig. 1 (Wilson and Javitt). A subconjunctival bleb is raised by injecting 0.5 ml of balanced salt solution.

Fig. 2 (Wilson and Javitt). A 1.5-mm incision is made with a sharp blade in clear cornea.

W × 0.2 second) were used to create a scleral fistula. The tip of the sapphire probe, with its red helium-neon aiming beam, was seen in the subconjunctival space when the opening extended through the sclera. The adequacy of the sclerostomy was evident by the flow of hyaluronic acid from the anterior chamber into the subconjunctival space. The limbal incision was closed with a single suture of 10-0 nylon.

Postoperatively, each patient was treated with 1% prednisolone acetate every two hours while awake and one drop each of 1% tobramycin and 1% atropine four times a day. Ten subconjunctival injections of 5-fluorouracil were administered over a three-week period postoperatively. The course of 5-fluorouracil was shortened if there was corneal epithelial breakdown. The antibiotic was discontinued at ten days and atropine at three weeks. The corticosteroid was reduced to four times a day after four weeks, two times a day after eight weeks, and once a day after nine weeks, before discontinuing at ten weeks.

Case Reports

Case 1

A 90-year-old white man with advanced primary open-angle glaucoma after cataract extraction and mild, chronic uveitis had an intraocular pressure of 43 mm Hg, despite maximum medical therapy. A previous trabeculectomy had failed. On examination aphakia was noted and no vitreous was visible. Laser sclerostomy ab interno was performed and eight injections of 5 mg of 5-fluorouracil were given over the subsequent two weeks.

One week postoperatively, vitreous was noted in the anterior chamber, which occluded the filtering fistula. A pars plana vitrectomy was performed with transscleral drainage of choroidal detachments. An intraocular pressure of 5 mm Hg or less was noted over the next four weeks. At Week 5, however, an encapsulated

Fig. 3 (Wilson and Javitt). If the vitreous face has been ruptured, any visible vitreous must be removed.
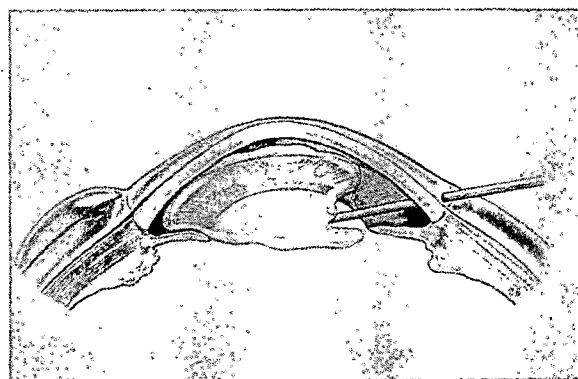
Fig. 4 (Wilson and Javitt). Hyaluronic acid is instilled into the anterior chamber and directed towards the site of the planned sclerostomy.
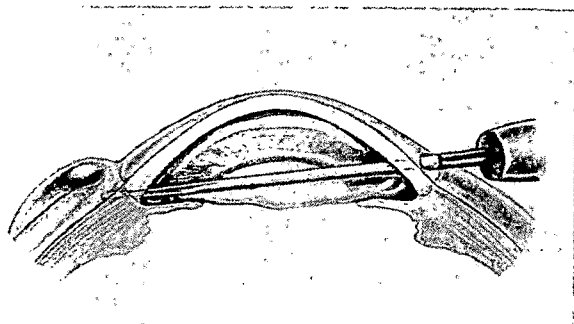
Fig. 5 (Wilson and Javitt). The sapphire laser probe is advanced across the anterior chamber and brought into contact with the sclera in the region of Schwalbe's line. Between three and five pulses of 800 mJ are required to achieve filtration.

bleb with a pressure of 17 mm Hg was noted. Failure of the bleb progressed over the subsequent four weeks with a pressure of 40 mm Hg by Week 10. Cyclophotocoagulation of the ciliary body was performed with good intraocular pressure control at 28 months (Fig. 6).

Case 2

A 52-year-old white man with primary open-angle glaucoma and advanced optic nerve loss that was controlled poorly with medical therapy was examined three weeks after extracapsular cataract extraction without intraocular lens insertion. Although the patient had no history of uveitis before cataract extraction, intraocular pressure was 38 mm Hg and examination disclosed severe cell and flare. A wedge of swollen cortex was visible with an intact posterior capsule at slit-lamp examination.

After discontinuation of pilocarpine and a short but unsuccessful trial of hourly cortico-

steroids, the decision was made to remove residual cortex and attempt surgical filtration for control of intraocular pressure. Laser sclerostomy ab interno was performed, along with irrigation and aspiration of the remaining cortical material. A course of ten subconjunctival injections of 5-fluorouracil was administered over three weeks. At one week postoperatively, a low bleb and a pressure of 28 mm Hg were noted. Digital massage and topical timolol were instituted with immediate reduction in intraocular pressure. One week later, the pressure was 3 mm Hg and a diffuse bleb was noted. Massage and timolol therapy were discontinued. At five weeks, the pressure was 48 mm Hg and the bleb was lower. Massage and timolol therapy were reinstituted. Over the subsequent three weeks, the eye was noted to be less inflamed and corticosteroids were tapered (Fig. 7). Timolol was reduced to once daily in Week 6, and a controlled intraocular pressure of 13 mm Hg has been maintained with continued digital massage at 26 months.

Case 3

A 64-year-old white man had open-angle glaucoma and an intraocular pressure of 34 mm Hg on maximum tolerated medication. The patient had previously undergone intracapsular cataract extraction with subsequent insertion of an anterior chamber intraocular lens. When he developed secondary uveitis and glaucoma, a trabeculectomy was performed and the implant was removed. The filtering bleb subsequently failed and visual field examination showed only a central island of visual acuity remaining.

A pars plana vitrectomy was performed with laser sclerostomy ab interno. Over the first three postoperative weeks, 11 injections of 5-
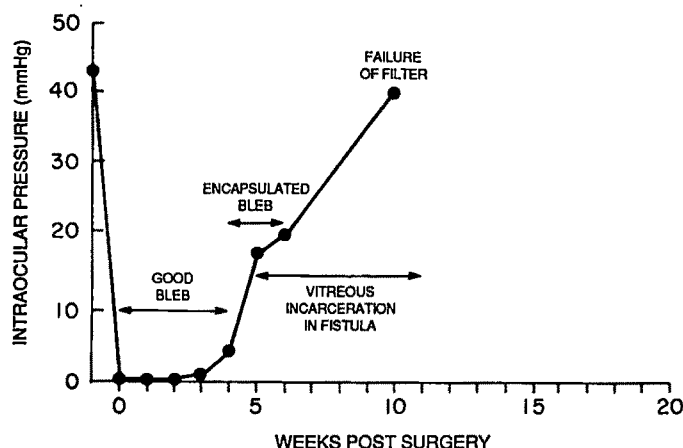
Fig. 6 (Wilson and Javitt). (Case 1.) Persistent choroidal detachments during the early postoperative period caused anterior displacement of vitreous with incarceration in the fistula. Subsequent failure of the bleb necessitated cyclodestructive procedure for pressure control.
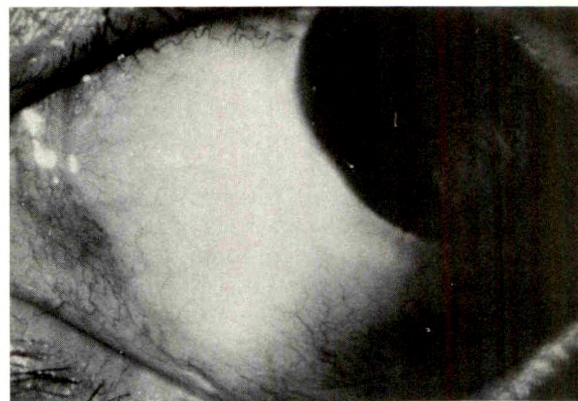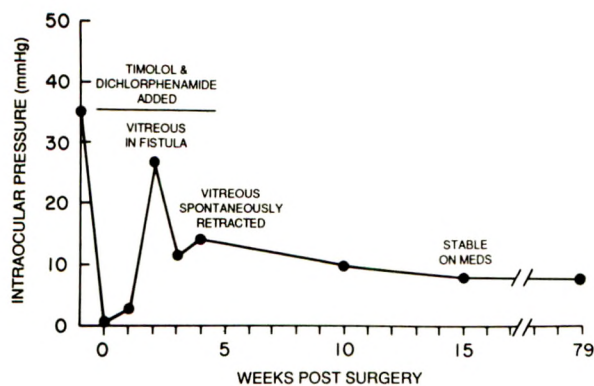
Fig. 7 (Wilson and Javitt). (Case 2.) Left, Cessation of digital massage during early postoperative period caused pressure increase. Re-institution of massage produced good pressure control with no medications. Right, A diffuse, avascular bleb can be seen at 20 months postoperatively.

fluorouracil were administered. Intraocular pressure remained at 10 mm Hg or below for the first five weeks. By Week 10, a pressure of 34 mm Hg was measured. Treatment with 0.5% timolol twice daily and 200 mg of methazolamide orally daily decreased the pressure to 19 mm Hg. At 4 months, however, the intraocular pressure had increased to 27 mm Hg, necessitating a ciliary body cyclophotocoagulation. The pressure is now controlled at 25 months.

Case 4

A 65-year-old white man had aphakia and a history of anterior segment neovascularization and chronic inflammatory glaucoma. He had previously undergone extracapsular cataract extraction with vitreous loss. Because of vitreous in the wound and cystoid macular edema, a

core vitrectomy was performed at a later date. Initial intraocular pressure was 32 mm Hg with maximum medical therapy. Extensive scarring of the superior conjunctiva was noted on examination.

Laser sclerostomy ab interno was performed and ten injections of 5-fluorouracil were administered over the subsequent three weeks. At Week 2 the intraocular pressure was 27 mm Hg. Previously unseen vitreous had been displaced forward by choroidal effusion and obstructed the fistula (Fig. 8). A retinal consultant suggested observation, and the vitreous was seen to retract by Week 3 with an intraocular pressure of 12 mm Hg. The bleb function continued to improve and the intraocular pressure at 24 months was 15 mm Hg with 25 mg of dichlorphenamide twice daily in the contralateral eye.
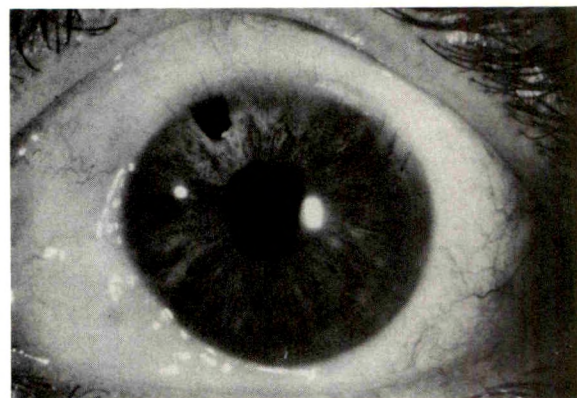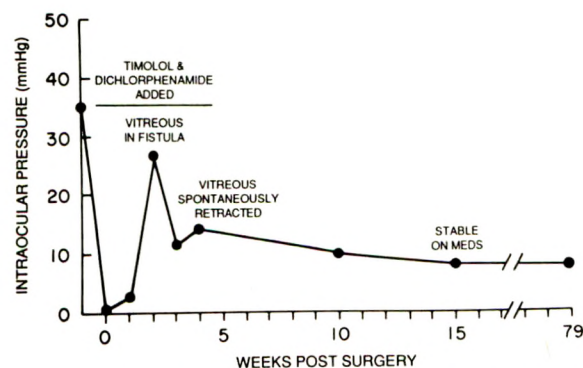
Fig. 8 (Wilson and Javitt). (Case 4.) Left, Choroidal detachments caused anterior displacement of vitreous with early occlusion of the fistula. As detachments resolved, the vitreous spontaneously retracted. Right, A diffuse, microcystic bleb can be seen at 19 months with no pressure-lowering medications.

Case 5

A 71-year-old white woman developed exacerbation of her primary open-angle glaucoma after an extracapsular cataract extraction with posterior chamber intraocular lens implantation, complicated by a large capsular tear. Vitreous in the superior anterior chamber and extensive conjunctival scarring made a trabeculectomy unfeasible. The preoperative intraocular pressure was 25 mm Hg with three topical medications. A laser sclerostomy ab interno was performed in the inferonasal quadrant and six injections of 5-fluorouracil were administered over the subsequent two weeks. Treatment with 5-fluorouracil was discontinued because of persistent corneal epithelial defects. A diffuse bleb was noted postoperatively. At six weeks, the patient had an intraocular pressure of 17 mm Hg with no pressure-lowering medications. Corticosteroids were tapered and intraocular pressure varied from 16 to 18 mm Hg at 24 months on 0.5% timolol twice daily.

Results

A total of five patients were treated with laser sclerostomy ab interno using the sapphire tipped Nd:YAG contact laser. Three of the five patients showed evidence of continued filtration with change in bleb size on massage and visible fistulas on gonioscopy. The mean follow-up time was 25.0 months (S.D. = 1.0 months). Mean intraocular pressure was 15.0 mm Hg (S.D. = 2 mm Hg) in the three patients with successful outcomes. An average decrease of 12 mm Hg (S.D. = 8.9 mm Hg) was noted when all patients were included. This decrease in intraocular pressure is statistically significant by paired t-test (P = .039)

One of the three patients with successful outcomes (Case 5) required the addition of timolol to maintain an acceptable pressure. A second patient (Case 4) required the continuation of dichlorphenamide as part of the therapy for the contralateral eye. Two patients (Cases 1 and 3) required a cyclodestructive procedure after failure of the filtering bleb at ten and 12 weeks postsclerostomy.

No intraoperative complications were noted in any patient. No corneal changes were noted as a result of the laser sclerostomy. The postoperative course was consistent with that of a full-thickness filtering procedure in an inflamed eye. Choroidal detachments were observed during the postoperative period in all patients and required drainage in one patient. In two patients, anterior choroidal detachments caused anterior displacement of previously unseen residual vitreous base. In one patient the vitreous caused failure of the sclerostomy. In the second patient, the vitreous retracted as the choroidal effusions resorbed and filtration was restored.

Discussion

The patients selected for this pilot series were those in whom traditional filtering surgery had failed or was deemed unfeasible. Extensive conjunctival scarring or recent surgery ruled out the use of the superior 180 degrees of limbal conjunctiva. Because all patients had surgical aphakia with chronic inflammation, a full-thickness filtering procedure with postoperative subconjunctival injection of 5-fluorouracil was indicated.

Given the poor prognosis in these patients, we found our results encouraging. Specifically, the intraocular pressure in one patient was controlled without medications; pressure in two was controlled with medications. The filtering fistulas failed in two patients. This is analogous to our experience with Schocket and Molteno shunts in similar cases. Since a standard, superior trabeculectomy was not appropriate for any of these patients, we cannot compare our success rate with that procedure.

In all patients, we were successful in creating a filtering fistula with no evidence of intraoperative complication. There was no evidence of thermal injury to surrounding ocular structures, especially iris and corneal endothelium. This is consistent with previous reports of ab interno laser sclerostomy in rabbit and primate models.[4,5,8-10]

The postoperative appearance was that of a full-thickness filtering procedure. Because there was no conjunctival suture line as would be expected with a limbal-based filtering procedure, subconjunctival diffusion was not limited and a lower, more diffuse bleb was observed. Choroidal effusions were expected because of the sudden decompression of an inflamed eye after an extended period of increased intraocular pressure. The choroidal effusions were comparable to those seen after other forms of full-thickness filtering surgery.

In two patients, the choroidal detachment

pushed the residual vitreous base forward into the anterior chamber. This caused filtration failure in the one patient who required drainage of choroidal effusions and the need for supplemental medication in another. In neither of these patients was vitreous visible on preoperative slit-lamp examination. However, this occurrence suggests that in patients with aphakia without an intraocular lens to hold back the vitreous, a more complete vitrectomy is warranted at the time of laser sclerostomy.

In the second patient with failed filtration, the cause of failure appeared to be closure of the scleral fistula. In patients with active inflammation and aphakia, a sclerostomy larger than 200 μm may be necessary to offer a better chance for long-term patency. Certainly early institution of massage may be helpful in maximizing flow through the fistula.

An alternative for these patients might have been secondary surgical trabeculectomy in the inferotemporal quadrant. Our success with this procedure has been limited, primarily because of postoperative closure of the fistula. The inferonasal quadrant is more appropriate for laser sclerostomy, since the fiberoptic is introduced at the temporal corneoscleral limbus and passed across the anterior chamber.

Another alternative might have been the use of a seton, such as the Molteno valve, the Shocket tube, or the Krupin-Denver valve. Although success has been reported with these devices in patients similar to those in our series, the implanting of a seton is a technically arduous surgical procedure, and the seton itself is a foreign body that may extrude or become a nidus of infection. In contrast, laser sclerostomy is generally completed in 15 minutes, although a vitrectomy may extend the procedure time by approximately 30 minutes. No foreign material is implanted. Should the laser sclerostomy fail, a seton procedure can still be attempted at a later time.

The trabecuphine has been tested in patients by Brown and associates[1] with some initial success. Since it cuts a tunnel through sclera and episclera, intraoperative hemorrhage can result from transected vessels. This can be difficult to control with external pressure or viscoelastic agents. If red blood cells and platelets are a stimulus to fibrosis, this may prove a long-term disadvantage to the trabecuphine approach.

March and associates[2,3] have succeeded in creating a filtering fistula by directing Nd:YAG energy through a contact lens. They reported

that this approach required 26,676 mJ for optimal perforations in eyes from eye banks. The fistula created had an internal opening of 100 μm. A substantial portion of the laser energy may well be scattered to areas other than the target tissue. With contact laser technology, a fistula with an external opening of 200 μm can be created with one eighth the amount of laser energy, an average of 3,600 mJ. Energy is delivered directly to the target tissue with minimum backscatter. This more efficient use of laser energy should produce less postoperative swelling and inflammation.

The continuous wave Nd:YAG laser, when optically coupled to a sapphire probe, has proven capable of establishing a laser sclerostomy ab interno. This technique offers three major advantages over conventional filtering surgery. Injury to conjunctiva and Tenon's capsule is slight and no suture or other foreign body is left to augment inflammation. This may decrease the tendency to episcleral fibrosis. Because there is no conjunctival section, the likelihood of a conjunctival wound leak is virtually nonexistent. This is of particular concern when antifibrosis agents, such as 5-fluorouracil, are to be used. The inferonasal quadrant, which is difficult to reach with conventional filtering surgery, is easy to reach with the contact laser.

The results achieved in patients with an extremely poor prognosis are encouraging. The likelihood of success at 18 months of follow-up compares favorably with that achieved through the much more complex implantation of Schocket and Molteno valves. The laser used has now been approved for clinical use and a larger series of patients with less severe glaucoma will further elucidate the strengths of this technique.

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OPHTHALMIC MINIATURE

Then he changed paws and repeated the identical process on the left: one pass over the whiskers, one pass over the cheekbone, twice over the eye, once over the brow, once over the ear, once over the back of the head.

Lilian Jackson Braun, *The Cat Who Could Read Backwards*
New York, Jove Books, 1966, p. 64

Biometric Variables in Patients With Occludable Anterior Chamber Angles

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Biometric studies of the ocular dimensions in eyes with narrow anterior chamber angles provide insight into the pathophysiology of pupillary block and may show which eyes are more prone to develop angle-closure glaucoma. We reviewed the records of 56 patients with occludable angles examined between 1980 and 1984. Initial biometric data obtained on the patients included corneal diameter, anterior chamber depth, lens thickness, and ocular axial length. The average length of follow-up was five years. Of 54 patients with complete clinical records, 20 (37%) eventually required peripheral iridectomy after a mean duration of 16 months from the initial examination. Cox's survival analysis showed a strong correlation between shortened duration to peripheral iridectomy and increasing lens thickness/ocular axial length ratio factor (P = .03). No other variables were significantly related to outcome. This suggests that the lens thickness/ocular axial length ratio may be useful as a predictor of clinical outcome in narrow-angle glaucoma.

BIOMETRIC STUDIES of the ocular dimensions of eyes with narrow-angle glaucoma have provided insight into the pathophysiologic aspects of pupillary block, iris bow, and resultant angle closure. These studies have shown that, compared to normal eyes, the angle-closure eye has a smaller corneal diameter,[1,2] smaller radius of anterior corneal curvature,[2,3] smaller radius of posterior corneal curvature,[4] shallower anterior chamber,[5] smaller radius of anterior lens curvature,[6] thicker lens,[1,2] lens that is situated relatively more anteriorly,[5] shorter ocular axial length,[1,2] and a decreased anterior chamber volume.[7] Markowitz and Morin[8] found that the lens thickness to ocular axial length ratio was greater than normal for most age groups with acute angle-closure glaucoma. They hypothesized that this factor defined the relationships between the lens, iris, cornea, and, thus, the status of the chamber angle.[8]

We investigated the correlation between early biometric variables, such as lens thickness to ocular axial length ratio, in patients with narrow occludable chamber angles and the later development of angle-closure glaucoma or the need for peripheral iridectomy.

Patients and Methods

A total of 56 patients with clinically determined occludable anterior chamber angles were examined by one of us (R.E.C.) between August 1980 and March 1984. Initially each patient underwent complete ocular examination including refraction, keratometry readings, slit-lamp and fundus examination, gonioscopy, and applanation tonometry.

Biometric measurements were also performed on each eye. Corneal diameter was determined by a handheld rule. Measurements of anterior chamber depth, lens thickness, and ocular axial length were obtained by immersion technique, A-scan ultrasonography. Tissue recognition of anatomic structures allowed automatic measurement of the tested variables. A specular microscope was used in conjunction with a video recording system to obtain pachymetry readings and endothelial cell counts.

The records of these patients were reviewed from the initial examination to the final follow-up visit. Specific information derived from the

records included symptoms of intermittent angle closure, gonioscopic evidence of narrowing or chronically closed angle, history of an acute angle-closure attack, and the clinically determined need for peripheral iridectomy to control narrow-angle glaucoma. The criteria to perform peripheral iridectomy were based on the gonioscopic appearance of the angle in combination with clinical symptoms, without knowledge of the biometric data.

To eliminate bias, only one randomly selected eye from each patient was included in the biometric and chart review analysis. A lens thickness/ocular axial length index was formulated for each eye[8] and included with other biometric variables in statistical analysis. This index was obtained by multiplying the ratio by ten to provide numbers with values of one or more.

Fifty-six patients had adequate biometric data to allow intervariable correlation analysis by linear regression. Fifty-four patients had sufficient clinical data for analysis. Forty-seven patients had complete biometric and clinical data to allow a stepwise logistic regression to determine the relationship, if any, between the initial biometric variables and the eventual need for peripheral iridectomy.

Kaplan-Meier survival analysis was performed on the duration of follow-up and duration to peripheral iridectomy on all eyes with complete biometric and clinical data. Peripheral iridectomy was the only criterion for failure. Eyes were considered removed from survival analysis if they underwent cataract extraction. Further analysis of the data was performed by using Cox's analysis with covariates of age and lens thickness/ocular axial length ratio to determine the effect of these variables on the time

interval between entry into the study and peripheral iridectomy. A P value of less than .05 was considered statistically significant.

Results

A total of 56 patients (56 eyes) were examined. The average age was 64 years (S.D. = ±10.6). There were 11 men (20%) and 45 women (80%). Of the 56 eyes, 33 (59%) were right eyes and 23 (41%) were left eyes. Fifty-four patients (54 eyes) had sufficient clinical data to be evaluated (Table 1). Of these 54 patients, 20 (37%) eventually required peripheral iridectomy to control narrow-angle glaucoma as determined by the clinical criteria of one of us (R.E.C.) without knowledge of the biometric data, eight (15%) had symptoms of angle closure, one (2%) had an acute angle-closure attack, six (11%) had chronic angle closure, five (9%) had narrowing angles, and nine (17%) had cataract extraction.

All biometric study variables were not recorded in certain cases, which gave a different sample size than 56 for the affected measurements (Table 2). There were numerous strong correlations in linear regression analysis (Table 1). There was strong evidence that the lens thickness/ocular axial length factor increased with age and that an increased lens thickness was associated with a decreased anterior chamber depth.

Kaplan-Meier survival analysis of the group

TABLE 1

SIGNIFICANT CORRELATIONS BETWEEN SELECTED
BIOMETRIC VARIABLES IN EYES WITH NARROW
ANTERIOR CHAMBER ANGLES

CORRELATIONS	P VALUE
Positive	
Lens thickness and age	.010
Lens thickness/ocular axial length ratio and age	.003
Anterior chamber depth and axial length	.010
Negative	
Spherical equivalent and keratometry	.010
Spherical equivalent and axial length	.005
Corneal diameter and keratometry	.010
Axial length and keratometry	.001
Anterior chamber depth and lens thickness	.020

TABLE 2

BIOMETRIC VARIABLES OF EYES WITH NARROW
ANTERIOR CHAMBER ANGLES

VARIABLE	NO. OF EYES	MEAN	S.D.
Spherical equivalent (diopters)	56	+1.40	2.50
Keratometry (diopters)	56	43.96	1.72
Corneal diameter (mm)	56	10.70	0.47
Tonometric reading (mm Hg)	52	16.30	4.90
Endothelial cell count (cells/mm²)	28	2348.00	556.00
Pachymetry (mm)	36	0.55	0.04
Anterior chamber depth (mm)	50	2.40	0.26
Lens thickness (mm)	49	5.09	0.36
Ocular axial length (mm)	51	22.34	1.00
Lens thickness/ocular axial length ratio factor	47	2.27	0.17
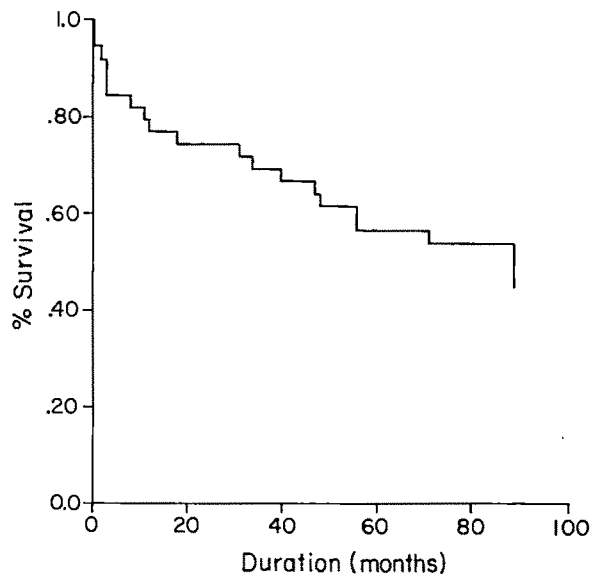
Fig. 1 (Panek and associates). Kaplan-Meier survival analysis of the group of patients with narrow-angle glaucoma showing cumulative proportion surviving (not requiring peripheral iridectomy) over time.

Fig. 2 (Panek and associates). Cox's model survival analysis with estimated cumulative proportion of patients with narrow-angle glaucoma surviving (not requiring iridectomy), adjusting for lens thickness/ocular axial length ratio factor. Examples of factors 2.00 and 2.50 are given as illustration.

(Fig. 1) showed that the average time under observation was 62 months and the average length of time before peripheral iridectomy was required in affected eyes was 16 months. This analysis indicated that, theoretically, 60% of all of the patients studied would require iridectomy by 85 months. Cox's analysis with covariate of the lens thickness/ocular axial length factor showed a marked tendency toward earlier peripheral iridectomy with increasing value of the lens thickness/ocular axial length ratio factor (Fig. 2) (P = .03). This tendency was not age related and was not affected by elimination of patients from analysis after cataract extraction. No other biometric variables, including lens thickness or axial length alone, were statistically related to the outcome of peripheral iridectomy by using Cox's analysis.

Discussion

Eyes with pupillary block, angle-closure glaucoma have associated numerous distinct anatomic variations from normal, which include smaller corneal diameter, shallower anterior chamber, thicker lens, anteriorly displaced lens, shortened axial length, and a decreased anterior chamber volume.[1-7]

These factors are probably inherited in a polygenetic fashion in which a large number of genes interact to produce a total anatomic effect.[9] The predisposed eye, through long-term environmental changes and acute trigger mechanisms, may have an increase in relative pupillary block and subsequent acute angle-closure glaucoma.[9]

One chronic, gradual change that affects the narrow-angle eye is the progressive shallowing of the anterior chamber that occurs during adult life. This is caused almost entirely by increasing lens thickness.[10] When the dimensions of the chamber angle reach a critical point, the patient becomes susceptible to acute variations in chamber volume and relative pupil block, which makes angle closure more likely.[10]

Markowitz and Morin[8] showed that the lens thickness/ocular axial length ratio factor was useful as a representative and unifying unit for biometric assessment of the narrow-angle eye. They define the normal value as 1.91 (S.D. = ±0.44). They found this factor to be age-dependent and greater than normal in most age

groups with narrow-angle glaucoma. Biometric data from our present study correlate well with theirs. The lens thickness/ocular axial length ratio factor of 2.27 (S.D. = ±0.17) for this study group as a whole was greater than normal. The strong correlations between lens thickness and age and lens thickness/ocular axial length ratio and age support the concept of a lens-related progressive shallowing of the anterior chamber.

Cox's analysis of the data from this study group indicated that an increasing lens thickness/ocular axial length ratio correlated with a decrease in duration in time to the need for peripheral iridectomy. This evidence supports the conclusion that a combination of increased lens thickness and a shortened eye is an important precipitating factor in pupillary block, angle-closure glaucoma. Additionally, it implies that this factor may be useful in predicting eyes that are most likely to require iridectomy.

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A Double-Masked Three-Month Comparison Between 0.25% Betaxolol Suspension and 0.5% Betaxolol Ophthalmic Solution

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In 352 patients with primary open-angle glaucoma or ocular hypertension, a multicenter double-masked, parallel-group clinical study compared the effects on intraocular pressure and ocular comfort of 0.5% betaxolol ophthalmic solution, a cardioselective beta-adrenergic blocking agent, with 0.25% betaxolol suspension. With twice-daily dosages, baseline intraocular pressure was significantly reduced ($P = .0005$), with no significant difference between the two groups, at Week 2 and at Months 1, 2, and 3. Further, the prevalence of ocular discomfort upon topical instillation was significantly lower for 0.25% betaxolol suspension than for 0.5% betaxolol solution ($P = .0005$).

NUMEROUS REPORTS HAVE DESCRIBED a wide range of adverse clinical effects from systemic absorption of topically administered beta-adrenergic blocking agents on pulmonary and cardiovascular functions.[1-11] In contrast to the nonselective beta-adrenergic blocking agents, betaxolol, a cardioselective beta-adrenergic blocking agent, has been shown to have fewer systemic side effects while effectively decreasing intraocular pressure.[12-19] A new ophthalmic delivery vehicle has been developed, which allows a twofold reduction in the concentration of topically administered betaxolol without an effect on the drug concentration in rabbit aqueous humor (unpublished data). In this new vehicle, 0.25% betaxolol has been formulated as a suspension. We compared the effects on intraocular pressure and ocular comfort of 0.5% betaxolol ophthalmic solution and 0.25% betaxolol suspension.

Patients and Methods

A formulation of betaxolol was developed in which 0.25% of betaxolol was suspended in microscopic (5-μm diameter) beads consisting of a polymer resin. In this form, betaxolol is released more slowly and gradually than in solution.

The 0.25% betaxolol suspension was compared with 0.5% betaxolol ophthalmic solution in a three-month, double-masked, randomized, parallel-group study. A total of 352 patients with primary open-angle glaucoma or ocular hypertension were enrolled by 24 investigators in this multicenter study. Approval of the Human Subject Committee of each institution was obtained before the study; informed consent was obtained from patients meeting enrollment criteria.

Before enrollment, patients who were receiving a single ocular hypotensive medication underwent a washout period (two weeks for beta-adrenergic blocking agents or epinephrine products, 48 hours for pilocarpine). The number of patients previously receiving beta-blocking agents was equal in the two groups studied.

After washout, baseline intraocular pressure measurements were taken at approximately 8:00 A.M. on two separate days, not less than three days apart. On the first baseline day, intraocular pressure was also measured at 4:00 P.M. Patients were included if each of the two morning measurements were greater than 24 mm Hg in at least one eye.

Patients were excluded from participation in the study if they had a recent history of ocular trauma, infection, or inflammatory diseases; an abnormality preventing reliable applanation tonometry; or a history of retinal detachment, diabetic retinopathy, intraocular surgery in the previous six months, contact lens wear, congestive heart failure, chronic obstructive pulmonary disease, use (within 30 days) of a systemic medication that could affect intraocular pressure (including alpha-adrenergic, beta-adrenergic, and calcium channel blockers), or hypersensitivity to betaxolol or to any formulation component. Pregnant or nursing women and women of childbearing potential who were not using adequate contraceptive methods were also excluded.

After enrollment, patients were randomly assigned in equal numbers to either the 0.25% betaxolol suspension or the 0.5% betaxolol solution group. At 8:00 A.M. on Day 0 of the study, the following data were recorded: demographic information, medical history, resting pulse rate and blood pressure, visual acuity, intraocular pressure, slit-lamp biomicroscopy, and cup/disk ratios.

After the baseline measurements, one drop of coded medication was instilled into each eye by the investigator. Patients returned eight hours after the dosage for intraocular pressure measurements. The medications were then dispensed to the patients, who were instructed to administer the eyedrops every 12 hours. Patients returned after two weeks, one month, two months, and three months, at which times their intraocular pressure (12 hours after dosage), visual acuity, ocular signs and symptoms, and resting pulse and blood pressure were measured. On each of these examination days, one drop of the study medication was instilled by the investigator in each eye after the morning examination, and intraocular pressure was measured again eight hours later.

Analyses of variance were used to compare the two treatment groups at eight hours and at 12 hours after dosage regarding changes from the baseline measurements in intraocular pressure, pulse rate, and mean blood pressure. Patients' comments referring to burning, sting-

ing, and discomfort upon administration of the eyedrops were combined and considered as ocular discomfort. Included in this category were reports of discomfort considered related, possibly related, and not related to the study medication. Chi-square was used to test for differences between the two treatments in the prevalence of ocular discomfort and blurred vision.

Results

The demographic characteristics of the patients enrolled in this study are summarized in Table 1. The mean intraocular pressure values for both treatment groups were significantly decreased from their respective mean baseline values ($P = .0001$ to $.004$) for each examination during the three-month study (Figure and Table 2). There was no significant difference in intraocular pressure between the two treatment groups at the Week 2 and Month 1, 2, and 3 examinations. Twelve hours after instillation of the eyedrops on the Month 3 examination, mean intraocular pressure was reduced for both groups from an 8:00 A.M. baseline reading of 26.0 mm Hg to 22.4 mm Hg (Figure). Eight hours after dosage at three months, mean intra-

TABLE 1
DEMOGRAPHIC CHARACTERISTICS OF 352 PATIENTS

	0.25% BETAXOLOL SUSPENSION	0.5% BETAXOLOL SOLUTION
Total number of patients entering study	180	172
Age (yrs), mean ± S.D.	58.6 ±13.9	59.4 ±13.3
Male	90	83
Female	90	89
Iris color		
Black/brown	80	87
Hazel/green/gray	39	36
Blue	61	49
White	141	129
Nonwhite	39	43
Black	27	32
Hispanic	11	11
Asian	1	0
Diagnosis		
Primary open-angle glaucoma	88	85
Ocular hypertension	92	87
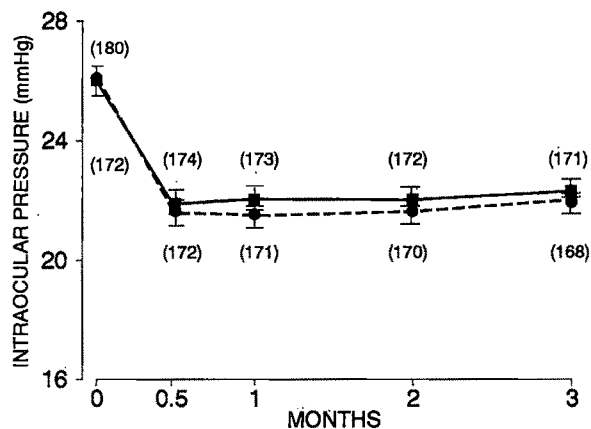
Figure (Weinreb and associates). Mean intraocular pressure (±S.E.), 12 hours after 8:00 A.M. dosage, of patients with primary open-angle glaucoma or ocular hypertension during three-month treatment with 0.25% betaxolol suspension (solid line and squares) or 0.5% betaxolol solution (dashed line and circles). Numbers in parentheses indicate the numbers of patients examined at each time. Mean intraocular pressure reduction from baseline was significant (P = .0001) for both treatment groups; the differences between treatment groups were not significant.

ocular pressure was reduced from a 4:00 P.M. baseline value of 23.9 mm Hg to 19.7 mm Hg in the 0.5% solution group and to 19.2 mm Hg in the 0.25% suspension group (Table 2).

Of the 352 patients examined for ocular comfort, 24 of a total of 180 patients (13%) in the 0.25% betaxolol suspension group reported burning or stinging at some time during the study compared to 64 of the 172 patients (37%) in the 0.5% betaxolol solution group. This difference was statistically significant (P = .0008) (Table 3). Other than the difference in discomfort between the two groups, there was no statistically significant difference regarding ocular signs and symptoms (Table 3). No clinically significant changes from baseline and no statistically significant differences (P = .18) between the treatment groups were observed regarding mean arterial pressure and pulse rate.

Fourteen patients in the 0.25% betaxolol suspension group and nine patients in the 0.5% betaxolol solution group did not complete the study, most for reasons unrelated to the medication. In the 0.25% suspension group, nine patients discontinued the study for reasons unrelated to the medication, two for uncontrolled intraocular pressure, two for ocular discomfort, and one for eyelid margin infection. In the 0.5% solution group, three patients discon-

tinued the study for reasons unrelated to the medication, four for uncontrolled intraocular pressure, one for asthma, and one for light-headedness.

TABLE 2
MEAN INTRAOCULAR PRESSURE EIGHT HOURS AFTER DOSAGE*

	0.25% BETAXOLOL SUSPENSION (MM HG)			0.5% BETAXOLOL SOLUTION (MM HG)		
	NO.	MEAN	(S.D.)	NO.	MEAN	(S.D.)
Baseline	179	23.9	(±3.7)	171	23.9	(±3.6)
Week 2	175	19.7	(±3.8)	172	19.8	(±3.7)
Month 1	171	19.8	(±3.5)	168	19.6	(±3.7)
Month 2	172	19.2	(±3.6)	169	19.5	(±3.5)
Month 3	161	19.2	(±3.3)	166	19.7	(±3.6)

*Intraocular pressure reduction from baseline was statistically significant (P = .0001) for both groups at each examination; treatment group differences were not significant. Intraocular pressure was measured at 4:00 P.M., eight hours after medication administered by the investigator.

Discussion

In this double-masked, parallel-group clinical study of 352 patients with primary open-angle glaucoma or ocular hypertension, both 0.25% betaxolol suspension and 0.5% betaxolol solution reduced intraocular pressure. The 0.25% betaxolol suspension reduced intra-

TABLE 3
OCULAR SIGNS AND SYMPTOMS OF 352 PATIENTS

	0.25% BETAXOLOL SUSPENSION N = 180	0.5% BETAXOLOL SOLUTION N = 172
	NO. (%)	NO. (%)
Burning and stinging	24 (13.0)	64 (37.0)
Blurred vision	7 (3.9)	3 (1.7)
Ocular dryness	4 (2.2)	3 (1.7)
Superficial punctate keratitis	4 (2.2)	3 (1.7)
Foreign body sensation	3 (1.7)	6 (3.5)
Itching	3 (1.7)	1 (0.6)
Ocular discharge	3 (1.7)	2 (1.2)
Ocular pain	3 (1.7)	5 (2.9)
Tearing	3 (1.7)	7 (4.1)
Ocular inflammation	2 (1.1)	3 (1.7)
Photophobia	2 (1.1)	1 (0.6)

ocular pressure to the same extent as 0.5% betaxolol ophthalmic solution throughout this three-month study.

Although it has fewer side effects, 0.5% betaxolol solution has been reported to reduce intraocular pressure to a lesser extent than 0.5% timolol or 0.5% levobunolol solutions, which are nonselective beta-adrenergic blocking agents.[20,21] It is well established that the topical administration of betaxolol is associated with fewer systemic side effects, particularly cardiopulmonary, compared with these other agents.[11-18] It has been used safely for prolonged periods of time in patients with even moderate chronic obstructive pulmonary disease and bronchial asthma.[14-18] The lowered concentration of the 0.25% betaxolol suspension would appear to provide an added margin of safety.

In addition to having the same intraocular pressure-lowering effect and safety profile as the 0.5% solution, the 0.25% suspension is better tolerated. Only 13% of the patients who received the suspension had burning or stinging, compared with 37% in the solution group. The greater ocular comfort of the suspension formulation is thought to be attributable not only to its lower concentration but because the active drug is delivered slowly, rather than in one bolus, thus having a lower potential for producing local irritation.

Despite the relative safety of betaxolol, however, the potential for any drug having a side effect must be considered. Thus, it is important to obtain a detailed medical history of each patient and to monitor symptoms throughout treatment.

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Microbial Contamination of Contact Lens Storage Cases and Solutions

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We compared microbial contamination of contact lens storage cases of asymptomatic contact lens wearers (Group 1; No. = 118; sampled once) and of contact lens wearers with manufacturer's lens-care instructions reinforced (Group 2; No. = 62; sampled three, six, 12, and 20 weeks after initial advisement). A significantly higher incidence of contamination of contact lens storage cases and solutions was observed among samples from Group 1 (132 of 247 samples) as compared to samples from Group 2 (30 of 500 samples; P = .000). Contact lens storage cases of individuals in Group 2 who used hydrogen peroxide systems (four of 78) showed a significantly lower incidence of contamination as compared to individuals who used other chemical disinfection (11 of 62 soft lens users; 10 of 59 rigid gas-permeable lens users; P = .041). Biofilms, adhered microorganisms embedded in a glycocalyx, in contact lens storage cases were not always inactivated by the addition of fresh solutions. Cleaning and periodic replacement of contact lens storage cases is recommended.

Donzis and associates[1] found that some elements of the contact lens care system of 52 of 100 asymptomatic patients were contaminated with microorganisms. The frequency of contamination was higher with systems for extended-wear lenses compared to daily-wear lenses, presumably because the extended-wear solutions were used for a longer period of time. Bowden and associates[2] further implicated aged disinfecting solutions in combination with extended-wear lens use as a factor in 15 of 24 patients with microbial keratitis. Studies in our laboratories have also associated contact lens wear and the use of contaminated solutions with infections of the outer eye.[3-6] The organisms occurring in the contaminated solutions were shown to be the same strains that caused conjunctivitis or corneal ulcers of the patients. Certain organisms that can cause infections have a tendency to attach to surfaces of lenses and form biofilms.[7] Further, biofilms have been shown to have resistance to some chemical preservatives,[8] which results in increased risk of infection.[9] The selective populations of patients and the retrospective nature of most analyses have not permitted the extrapolation of data on the incidence of use of contaminated solutions to the general population of contact lens users. We compared contamination of solutions and storage cases that occurred among contact lens wearers who have and have not had lens-care instructions reinforced.

Material and Methods

Samples of contact lens storage cases and solutions were collected from asymptomatic contact lens wearers who represented two populations: individuals who had contact lenses that were dispensed elsewhere and had not been advised by us about lens care and hygiene; and individuals who were advised by us on proper lens care and hygiene.

Group 1 consisted mostly of individuals visiting the Contact Lens Service of the Emory Eye Center for the first time and of students at Georgia State University. Samples were not collected on a set day or at a set time after

disinfection of lenses. There was no specific selection of subjects on the basis of sex, age, race, economic status, or usage of a particular disinfection regimen, except heat disinfection was not included in this study. All samples of lens care solutions collected were within the indicated expiration date on the container. If any solutions were found to be contaminated, the contact lens wearer was contacted, advised of proper lens care, and their care systems replaced.

Group 2 was composed of 62 daily-wear contact lens users who were recruited from Group 1. These contact lens wearers were assigned to three subgroups: hydrogen peroxide disinfection systems for soft lenses (22 users); other chemical disinfection systems for soft contact lenses (20 users); and chemical disinfection systems for rigid gas-permeable contact lenses (20 users). Individuals were provided with a new unit of their lens care system and were instructed to disinfect and store the lenses every night according to the manufacturer's regimen. Additionally, some individuals used a terminal aerosol rinse before lens insertion. The lens storage case with lenses stored in catalytic disk-neutralized H_2O_2, the disk itself (where applicable), or H_2O_2-neutralizing solution were cultured on all visits to the clinic. Disinfection solutions in the storage case and in the parent bottles and commercially prepared saline rinsing solutions (preserved and preservative-free) were also cultured for microorganisms on all visits to the clinic. Clinic visits were scheduled for a day after overnight disinfection of lenses during Weeks 3, 6, 12, and 20 after initial advisement. The contact lenses were removed for wear immediately after culture of the storage case and its solutions. Solutions and storage cases that were found to be contaminated were replaced with a new unit. Manufacturer's lens-care instructions were reinforced on each visit.

All samples collected from individuals in both Group 1 and Group 2 were initially cultured on chocolate agar at 37 C. Parent containers that yielded microorganisms on initial culturing were resampled aseptically through the wall of the container by means of a syringe and needle. Bacteria were presumptively identified with the API 20E system (API Analytab Products, Plainview, New York); final identifications of bacteria and fungi were performed as described previously.[4-6] The data were analyzed statistically with the chi-square test.

Contact lenses and portions of storage cases

were prepared for scanning electron microscopy with the method of Simmons and associates.[9]

Results

Microorganisms were isolated from 34 of 51 (66%) solutions with preservatives and 28 of 28 (100%) preservative-free solutions in contact lens storage cases of individuals not advised by us (Group 1; Table 1). Among Group 2 individuals who used soft lenses, lens storage cases of four of 74 (5%) storing their lenses in neutralized H_2O_2 were contaminated, whereas seven of 66 (10%) lens storage cases of individuals who used other chemical disinfecting solutions were contaminated. Among users of rigid gas-permeable lenses, ten of 51 (19%) lens storage cases of individuals in Group 2 who used disinfectant-storage (soaking, conditioning) solutions were contaminated as compared to 20 of 31 (64%) among Group 1 individuals (Table 1).

TABLE 1

INCIDENCE OF MICROORGANISMS IN CONTACT LENS
SOLUTIONS USED

	SOFT LENS USERS (NO. CONTAMINATED/ NO. SAMPLES)		GAS-PERMEABLE RIGID-LENS USERS (NO. CONTAMINATED/ NO. SAMPLES)	
	GROUP 1	GROUP 2	GROUP 1	GROUP 2
Solutions in lens cases				
Disinfectant-storage	34/51	7/66	20*/31	10/51
Preservative-free	28/28†	4/74‡	8/8	—
Disinfectant-storage in containers	4/36	0/62	10/35	3/51
H_2O_2 solutions in containers	1/12	1/78	—	—
Preservative-free saline (aerosol)	2/5	5/118	—	—
Miscellaneous§	25/41	—	—	—
Total percentage	54%	4%	51%	13%

*Includes one polymethylmethacrylate lens user.

†Includes neutralized H_2O_2 and preservative-free saline.

‡Includes only lenses stored in neutralized H_2O_2 for 12 to 18 hours.

§Includes unknown solutions in bottles and cases and neutralized H_2O_2 solutions in cases with unknown time of last use but more than 24 hours.

On initial screening, microorganisms were isolated from four of 36 (11%) of the containers of the disinfecting solutions for soft lenses used by Group 1 individuals, but the samples withdrawn through the sides of the containers by aseptic technique were culture-negative. The microbial populations isolated from initial samples of parent containers were confined mostly to the rim of the orifice of the dispenser tip.

The containers for lens solutions for rigid gas-permeable lenses used by Group 1 individuals were sometimes contaminated with bacteria in densities of over 10^5 cells/ml, mainly *Serratia marcescens, Enterobacter cloacae,* and *S. liquefaciens.* Two solutions, one preserved with chlorhexidine gluconate and the other with benzalkonium chloride, were most often contaminated. The bacteria grew in new containers of these solutions after laboratory challenge with less than 10^3 cells. Three containers of these preserved solutions for rigid gas-permeable lenses used by Group 2 individuals became contaminated with over 10^5 cells/ml during use.

Four of the seven aerosol canisters of saline that were culture-positive on initial screening also yielded heavy densities of bacteria in at least three repeated tests. These four canisters were over half used but still produced a steady stream of saline with internal pressures of 4 to 22 lbs/in^2. Saline obtained by aseptic puncture sampling were culture-negative. Further examinations showed that the microbes were confined to the channels of the plastic pressure caps. Overall a significantly higher incidence of contamination of lens storage cases and solutions was observed among Group 1 individuals (132 of 247 [53%]) as compared to Group 2 individuals (30 of 500 [6%]; P = .000).

The miscellaneous category (Table 1) included storage cases with unknown storage solutions. Fifteen H_2O_2 disinfectant storage cases that yielded microorganisms on initial screening, but the time of last use was unspecified (but not in excess of one week), were also included in this group. Bacteria as well as fungi (representing the genera *Aspergillus, Cladosporium, Exophila,* and *Fusarium*) were isolated from the catalytic disks in these storage cases even after the addition of fresh H_2O_2.

Examination by culture and scanning electron microscopy of representative storage cases of participants who used systems other than H_2O_2 demonstrated the presence of adhered microorganisms (Fig. 1). Viable microorganisms could be isolated from such lens storage
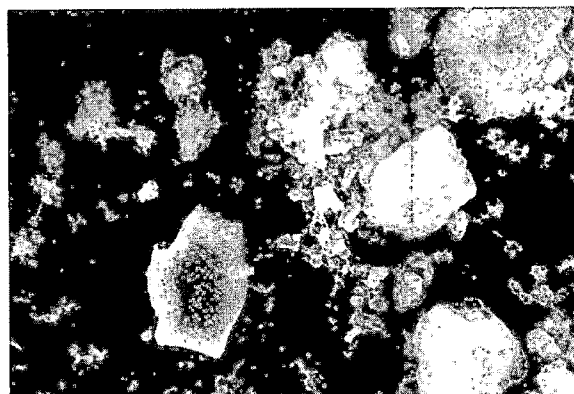
Fig. 1 (Wilson and associates). Adhered bacteria attached to the well surface of a contact lens storage case (× 1,400). *Serratia marcescens* was isolated from the storage case.

cases after the addition of fresh disinfectant solutions. Solutions were negative initially for microorganisms on culture but viable microorganisms could be demonstrated after vigorous swabbing and culturing of the storage case. Several cleaned and disinfected lenses stored in such storage cases developed biofilms of microorganisms (Fig. 2).

The common bacteria isolated from solutions in lens storage cases are listed in Table 2. Most storage cases that were used with soft lenses yielded gram-positive cocci, typically less than 10 colony forming units from a swab streak, but confluent growth was observed occasionally. Representative colony types were identified as
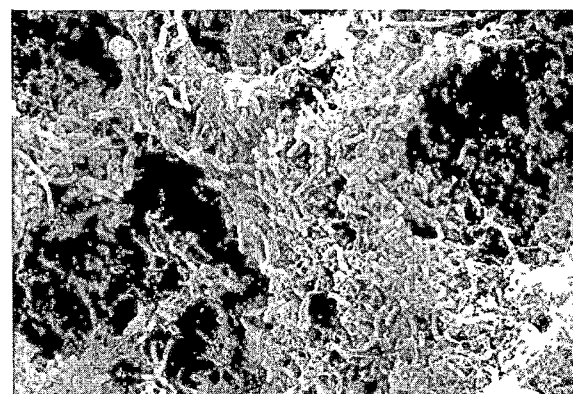
Fig. 2 (Wilson and associates). Bacteria and fungal cells adhered to the surface of a soft contact lens that was removed from the eye and placed in a contact lens storage case with fresh soaking and wetting solution (× 2,900). *Pseudomonas aeruginosa* was isolated from the solution in the storage case.

TABLE 2
BACTERIA COMMONLY ISOLATED FROM
CONTAMINATED LENS CASES*

	ISOLATES (%)	
MICROORGANISM	PRESERVED SOLUTIONS (NO. = 71)	PRESERVATIVE-FREE SOLUTIONS (NO. = 40)
Gram-positive cocci	59	58
Pseudomonas aeruginosa	18	40
Serratia sp.	34	10
Klebsiella sp.	6	0
Enterobacter sp.	6	38
Other gram-negatives	18	58

*Microbial identification not performed for all isolates from contaminated cases. Number of cases with microorganisms; more than one microorganism may have been isolated from a single contact lens case.

Staphylococcus epidermidis and Micrococcus species. Preservative-free solutions in storage cases more often yielded mixed growth dominated by Pseudomonas aeruginosa and other gram-negative rods. Heavy to confluent growth along the swab streaks was commonly observed with cultures from the preservative-free solutions. Except as indicated previously for certain catalytic disks, only occasional colonies of fungi were isolated from the samples of Group 1 individuals and none were obtained from samples from Group 2 wearers.

There was no statistically significant difference in the incidence of contamination of lens care paraphernalia between the first, second, third, and fourth clinic visits by Group 2 individuals, nor was there a statistically significant

difference in contamination observed between H₂O₂ systems, other cold disinfecting systems for soft lenses, and disinfecting systems for rigid gas-permeable lenses (Table 3). In Group 2, 24 of the 62 individuals had contaminated solutions in either the storage case, the parent container, or both, during the course of this study. Lens storage cases of individuals using H₂O₂ systems showed a lower incidence of contamination (four of 78 lens storage cases sampled) as compared to individuals who used other chemical disinfection systems (11 of 62), a difference statistically significant at the 5% level (Table 4).

Discussion

Previous investigations[1-6] have associated conjunctivitis and keratitis with the use of contaminated contact lens solutions. Our current findings correspond with Donzis and associates[1] and demonstrate that the use of contaminated solutions by asymptomatic contact lens wearers is not uncommon. In addition to preservative-free solutions that were typically contaminated, ten of 25 (40%) of the parent containers of the rigid gas-permeable soaking and wetting solutions preserved with chlorhexidine hydrochloride and benzalkonium chloride collected from Group 1 individuals were contaminated. These solutions have previously been shown to support the growth of microorganisms, especially Serratia species.[6] Most disinfection or soaking and wetting solutions in their original containers were inhibitory to microorganisms, but the efficacies of the solutions

TABLE 3
INCIDENCE OF CONTAMINATION OF LENS CARE SYSTEMS IN GROUP 2

LENS CARE SYSTEM	LENS TYPE*	NO. OF USERS WITH CONTAMINATED SYSTEMS†/ NO. OF USERS	VISIT (WKS) (NO. SYSTEMS CONTAMINATED/ NO. SAMPLED)				CONTAMINATED VISITS/ TOTAL VISITS
			3	6	12	20	
H₂O₂	Soft	7/22	0/22	3/19	2/19	3/18	8/78
Disinfectant-storage	Soft	9/20	5/20	3/18	2/13	3/11	13/62
Disinfectant-storage	RPG	8/20	4/20	3/16	1/12	2/11	10/59
Percent		39%	16%	17%	11%	20%	16%

*RPG indicates rigid gas-permeable lenses.
†Solution contamination in the case, the parent bottle, or both, of the lens care system was considered contamination of system.

TABLE 4
INCIDENCE OF CONTAMINATION OF INDIVIDUAL COMPONENTS OF LENS CARE SYSTEMS IN GROUP 2

		CONTAMINATED (%)			
LENS CARE SYSTEM	NO. SAMPLED	PARENT DISINFECTANT CONTAINER	PRESERVATIVE IN SALINE RINSE	PARENT SALINE CONTAINER	STORAGE CASE*
Soft Contact Lenses					
H₂O₂/disk	40	0	None†	10	8
H₂O₂/catalase	30	0	None	0	3
H₂O₂/pyruvic acid	4	25	—	—	0
H₂O₂/Na₂S₂O₃	4	0	None	0	0
Polyaminopropyl biguanide (PAPB)	18	0	PAPB	6	39
Chlorhexidine gluconate	27	0	None	4	15
Polyquaternium	17	0	None	0	0
Rigid Gas-Permeable Contact Lenses					
Chlorhexidine gluconate	16	12	—	—	25
Benzalkonium chloride	11	9	None	0	27
Thimerosal	24	0	—	—	13
Chlorhexidine gluconate + thimerosal	8	0	—	—	0

*All storage cases sampled contained either disinfectant or neutralized H₂O₂.
†Preservative-free aerosol.

were compromised in the lens storage cases. Individual practices such as failure to clean lenses and storage cases routinely, the addition of fresh fluids (including preservative-free saline and tap water) to residual fluids in storage cases, and periodic storage of lenses for varying periods between disinfection and insertion appeared to be major factors. Storage resulted in high densities of microorganisms in storage cases and the subsequent attachment of the microorganisms to the lenses. Microorganisms adhere to lenses rapidly and are not easily removed by rinsing.[7,9,10] The use of an aerosol saline stream should facilitate lens rinsing provided the stream is not contaminated. Conditions that precipitated the development of biofilms in the dispensing nozzles of seven of 123 aerosol canisters are unknown. A pseudomonad corneal ulcer has been associated with the use of an inappropriately maintained can of aerosol saline.[11]

In selected storage cases, bacteria were observed in biofilms. Biofilms may not always be inactivated when fresh disinfectant or preserved solutions are added to the lens storage case. Other studies have shown that the glycocalyx protects microorganisms from the action of some disinfectants.[8] The development of the biofilms seemed related to individual hygienic practices, because in study groups certain individuals were prone to develop contaminated storage cases repeatedly. In general, the incidence of potentially hazardous contamination among Group 2 (whose adherence to manufacturer's regimen was reinforced) was markedly less than that found for the Group 1 individuals. This finding suggests lapses in lens-care hygiene.

Penley and associates[12] have demonstrated that hydrogen peroxide was effective for the disinfection of contact lenses. Neutralized H₂O₂ solutions were found to become contaminated during lens storage. In the storage case of one system that used a platinum disk for neutralization, viable microorganisms were cultured from some disks from storage cases with stored lenses. Microorganisms reside on the disk because the decomposition of H₂O₂ in contact with the disk is instantaneous. The disk and storage case should be kept dry when not in use.

Manufacturers' regimens for contact lens cleaning and disinfection do not directly address hazards of storage as determined by this study. We recommend that regimens be modified to warn that the disinfection step should be repeated before lens insertion if more than 12 hours have lapsed since disinfection. Further, we suggest that storage containers for lenses be regularly cleaned, disinfected with heat or hydrogen peroxide (nonneutralized), and replaced periodically, ideally at each purchase of new disinfection solution.

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Potential Bacterial Contamination in Fluorescein-Anesthetic Solutions

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To determine the ability of fluorescein-anesthetic combination solutions and their applicators to regain sterility, we contaminated four commercially available fluorescein-anesthetic solutions and their dropper tips with inocula of either Pseudomonas species or Staphylococcus species. No organisms could be cultured from Fluress one minute after inoculation of the solution or five minutes after inoculation of the dropper tip. In contrast, organisms were cultured from the other fluorescein-anesthetic preparations for at least one hour after bacterial inoculation into the solution or onto the dropper tip. These differences in the ability of fluorescein-anesthetic solutions to regain sterility after bacterial contamination were statistically significant.

F LUORESCEIN SOLUTIONS used in ophthalmology have been a potential source of bacterial spread because of the propensity of *Pseudomonas aeruginosa* to grow in these solutions.[1] The introduction in 1966 of a fluorescein and benoxinate hydrochloride combination solution preserved with 1% chlorobutanol and made available in a glass bottle with a pipette dropper (Fluress) is thought to have greatly decreased this risk. The antimicrobial properties of this preparation have been extensively reported.[2-5] The importance of maintaining the dropper tip immersed in the solution has been demonstrated.[6] In recent years, other fluorescein-anesthetic solutions have become available from purveyors of generic pharmaceuticals. Although these are marketed as comparable or competitive to Fluress, they are neither pharmaceutical

equivalents nor pharmaceutical alternatives under the definitions of the United States Food and Drug Administration.[7] We undertook a laboratory evaluation of the relative resistance to contamination of several of these fluorescein-anesthetic products.

Material and Methods

Four fluorescein-anesthetic combination products were evaluated: pipette dropper bottles of Fluress (Barnes-Hind, Inc., Sunnyvale, California) containing fluorescein sodium 0.25%, benoxinate hydrochloride 0.4%, and chlorobutanol 1%, in a povidone plus boric acid solution; plastic squeeze dropper bottles of Fluorpro (Wilson Ophthalmic Corporation, Mustang, Oklahoma); and plastic squeeze dropper bottles and pipette dropper bottles of Fluorocaine (Akorn, Inc., Abita Springs, Louisiana). Both Fluorpro and Fluorocaine contain fluorescein sodium 0.25%, proparacaine hydrochloride 0.5%, and thimerosal 0.01% in a povidone plus glycerin solution. All bottles (Figure)
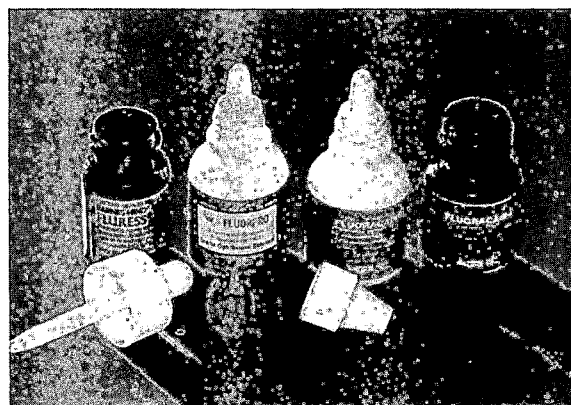
Figure (Duffner and associates). Fluorescein combination solutions are available in glass bottles with a glass dropper and in plastic squeezable bottles with an integral dropper tip.

were purchased from retail or wholesale drug suppliers. At least two different lot numbers for each preparation were included. All bottles were tested before their listed expiration date.

The bacterial inocula used were prepared from human ocular isolates of *P. aeruginosa* and *Staphylococcus aureus*. Suspensions of organisms were serially diluted to contain 100,000 colony forming units of bacteria per milliliter.

Eight bottles of each product were inoculated with 10 μl (approximately 1,000 organisms) of the *P. aeruginosa* suspension by placing a micropipette directly into the solution in the bottle. Single drops from each bottle were then dropped from the squeeze bottle or dropper onto sheep blood agar plates at one minute, five minutes, 15 minutes, one hour, two hours, and 24 hours after the solution was inoculated. Each drop was spread on the culture plate with a sterile cotton-tipped applicator. Plates were incubated at room temperature (25 C). After 48 hours, the colonies were counted. If there were too many colonies on a plate to count accurately, they were recorded as too numerous to count. One uninoculated bottle of each product was cultured as a negative control, and the bacterial suspension was directly cultured as a positive control.

Five bottles of each product were similarly inoculated with 10 μl (approximately 1,000 organisms) of the *S. aureus* suspension. Single drops were cultured after the same time intervals and incubated as above. Again, one uninoculated bottle of each product was cultured as a negative control and the bacterial suspension was directly cultured as a positive control.

Twenty-five bottles of each product were contaminated by placing 10 μl of the *P. aeruginosa* suspension directly onto the dropper tip or onto the bottle tip opening. Each bottle was then inverted five times. A sterile cotton-tipped applicator moistened with nutrient broth was used to wipe the bottle or dropper tip, and the applicator was streaked onto a sheep blood agar plate.

Five bottles of each product were cultured at one minute, 15 minutes, one hour, two hours, and 24 hours after intentional contamination of the tip. Positive and negative controls were cultured. These plates were incubated for 48 hours at 37 C and colonies were then counted.

Twenty-four bottles of each product were contaminated on the dropper tip or bottle tip opening with 10 μl of the *S. aureus* suspension. Four bottles of each product were similarly cultured using a broth-moistened cotton-

tipped applicator after one minute, 15 minutes, 30 minutes, one hour, two hours, and 24 hours. Positive and negative controls were cultured.

The arithmetic mean number of colonies was calculated for each set of plates. If one or more plates in a set had colonies that were too numerous to count, the set was recorded as too numerous to count. Statistical analysis of the data was performed using Dunnett's multiple comparison test if the numerical means were recorded, or the Mann-Whitney U-test with a Bonferroni correction if one or more sets had colonies too numerous to count.

Results

No organisms grew from any of the fluorescein, benoxinate hydrochloride, and chlorobutanol samples inoculated directly into the solution (Fluress). *Pseudomonas aeruginosa* and *S. aureus* were recovered from samples of the fluorescein sodium, proparacaine hydrochloride, and thimerosal solution (Fluorpro and Fluoracaine) up to two hours after inoculation (Table 1). The difference in mean colony counts between Fluress and each of the other three products was statistically significant for *P. aeruginosa* up to 15 minutes (P = .015) and for *S. aureus* after two hours (P < .05).

After inoculation onto the dropper tip or bottle tip, no *P. aeruginosa* grew from any of the Fluress samples. Of the four dropper tips contaminated with *Staphylococcus* and cultured after one minute, however, one bottle produced two colonies and one bottle produced one colony. *Staphylococcus aureus* did not grow from the other two Fluress dropper tips cultured after one minute, nor from any of the Fluress dropper tips cultured after more than one minute. There was growth of *P. aeruginosa* and *S. aureus* from samples of the other three products up to two hours after inoculation (Table 2). The difference from Fluress was significant up to 15 minutes after *P. aeruginosa* contamination for the Fluorpro samples and up to two hours for the Fluorocaine squeeze bottle samples (P < .05). The difference from Fluress after *S. aureus* contamination approached significance (P = .08) for up to two hours for the Fluorocaine squeeze bottle samples.

No bacteria were recovered from any uninoculated negative control bottle. Direct cultures of the bacterial suspensions, the positive controls, all produced confluent growth.

TABLE 1

MEAN COLONY COUNTS AFTER INOCULATION DIRECTLY INTO SOLUTION*

SOLUTION	TIME AFTER INOCULATION						
	1 MIN.	5 MIN.	10 MIN.	15 MIN.	1 HR.	2 HRS.	24 HRS.
Pseudomonas aeruginosa							
Fluress droppper bottle	0	0	0	0	0	0	0
Fluorpro squeeze bottle	TNTC	7.3	7.3	6.7	0.4	0	0
Fluorocaine squeeze bottle	TNTC	7.7	7.7	5.7	0.6	0	0
Fluorocaine dropper bottle	TNTC	2.7	2.7	3.3	2.4	0.5	0
Staphylococcus aureus							
Fluress dropper bottle	0	0	0	0	0	0	0
Fluorpro squeeze bottle	17.3	10.3	6.3	11.0	10.5	10.8	0
Fluorocaine squeeze bottle	26.8	7.3	7.0	13.3	12.5	6.3	0
Fluorocaine dropper bottle	2.0	5.5	1.8	2.5	5.8	3.0	0

*TNTC indicates too numerous to count.

Discussion

Although sterile paper strips impregnated with fluorescein may be used to instill fluorescein into the tear film, many ophthalmologists prefer the convenience of a combination fluorescein-anesthetic solution. Since the same bottle of solution is used on multiple patients, inadvertent contamination of the solution or the applicator could result in transmission of microorganisms from one patient to another. Prompt recovery of sterility after inadvertent bacterial contamination is an essential feature for a fluorescein-anesthetic solution. This study was designed to evaluate the ability of different commercially available preparations to regain sterility.

Although conducted in the laboratory, the components of the study were chosen to simulate the clinical setting. In clinical use, the dropper bottle tip is usually the entry point of the exogenous organism. Contamination of the dropper tip was therefore evaluated separately from contamination of the solution. Both plastic squeeze bottles and pipette dropper bottles were tested, because fluorescein-anesthetic solutions are available in each. The solution and dropper tips were evaluated at a variety of time periods after intentional contamination, as the time between consecutive uses of the container would vary clinically.

TABLE 2

MEAN COLONY COUNTS AFTER CONTAMINATION OF BOTTLE TIP OR PIPETTE TIP*

SOLUTION	TIME AFTER INOCULATION					
	1 MIN.	15 MIN.	30 MIN.	1 HR.	2 HRS.	24 HRS.
Pseudomonas aeruginosa						
Fluress dropper bottle	0	0	—	0	0	0
Fluorpro squeeze bottle	105.0	105.0	—	18.6	8.8	0
Fluorocaine squeeze bottle	80.6	94.0	—	64.0	42.6	0
Fluorocaine dropper bottle	23.0	11.6	—	2.6	0	0
Staphylococcus aureus						
Fluress dropper bottle	0.8	0	0	0	0	0
Fluorpro squeeze bottle	TNTC	4.8	1.5	4.3	7.5	0
Fluorocaine squeeze bottle	TNTC	TNTC	60.0	90.0	40.0	0
Fluorocaine dropper bottle	TNTC	11.3	TNTC	0.8	0.8	0

*TNTC indicates too numerous to count.

The fluorescein sodium, proparacaine hydrochloride, and thimerosal combination from either manufacturer (Fluoracaine or Fluorpro) did not regain sterility as quickly as the fluorescein, benoxinate hydrochloride, and chlorobutanol combination (Fluress) after either direct contamination of the solution with bacteria or after contamination of the tip of the container or the pipette dropper tip. This difference in ability to regain sterility after intentional contamination does not imply a defect in manufacture or storage of the products tested. Rather, it is probably because of differences in the properties of the combined components of the solutions.

Benoxinate hydrochloride preserved with chlorobutanol may be more resistant to contamination than proparacaine hydrochloride combined with thimerosal. Benoxinate hydrochloride and proparacaine hydrochloride are both excellent surface anesthetics; only benoxinate hydrochloride, however, has bacteriostatic properties.[8] Chlorobutanol and thimerosal are both commonly used as preservatives in ophthalmic solutions. Chlorobutanol has been shown to be a more rapid and effective preservative than thimerosal, which is characterized by its slow action.[8,9] Chlorobutanol, however, is an effective preservative only in an acidic solution (below pH 6), and can permeate through polyethylene bottles.[8] Therefore, it must be formulated precisely and stored in impermeable containers such as glass.

Differences in the other components of the two formulations may also contribute to the observed variations in performance. Boric acid, a component of Fluress, is weakly bacteriostatic,[10] whereas glycerin, a component of the other solutions, is not. Povidone is a dispersing, wetting, and stabilizing agent. It improves the fluorescent performance of these solutions.[11] Because it is a component of both of the formulations examined, it is not likely to account for the differences noted.

The fluorescein sodium, proparacaine hydrochloride, and thimerosal solutions (Fluorocaine, Fluorpro, and others) are generically equivalent to each other. Conversely, they are neither pharmaceutical equivalents nor pharmaceutical alternatives to a preparation of fluorescein, benoxinate hydrochloride, and chlorobutanol, and could thus be expected to have different properties. Drug products are considered pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration.[7,12] Drug products are

considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths.[7,12] Ophthalmologists using fluorescein sodium, proparacaine hydrochloride, and thimerosal solutions should be aware of their differences from the fluorescein, benoxinate hydrochloride, and chlorobutanol solution in packaging, anesthetic agent, preservative, vehicle, and ability to regain sterility. Our data demonstrate that bacteria can be cultured from fluorescein sodium, proparacaine hydrochloride, and thimerosal solutions for up to two hours after contamination.

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AMERICAN JOURNAL OF OPHTHALMOLOGY®

EDITORIAL

Cataract-Free Zone in Latin America

Francisco Contreras

According to the World Health Organization, age-related cataract is the cause of about 50% of the blindness in the world. This means that with a cataract extraction almost 18 million persons could recover their sight. Although this is a simple, effective, and inexpensive surgical procedure, only an estimated 10% of these patients are operated on. In the industrialized nations this challenge is being met and resolved successfully, but in the developing countries there are no prompt solutions.

Latin America is not far from this reality. Actually, we are 420 million inhabitants south of the Rio Grande River (Mexico), with 12,000 ophthalmologists, for a favorable ratio of 1/35,000 population. However, we are conscious of a significant distribution inequity. There are many rural areas and places surrounding urban areas that have limited medical resources, especially in the ophthalmologic field.

In September 1985, the Pan-American Association of Ophthalmology met with the National Eye Institute of the United States of America and, with the support of Helen Keller International, a nongovernmental organization, they designed an operation research program, called "Cataract-Free Zone." The purpose of this program was to reduce the backlog of those already blind from cataract in a target population living in a determined area, within a limited period of six months, by using appropriate technology that is relatively inexpensive, and with involvement of the community. In 1987 two geographic areas were chosen to demonstrate the feasibility of this program: the city of Chimbote, Peru, which has 183,000 inhabitants, and the underserved area of the city of Campinas, Brazil, with 100,000 inhabitants. Both locations had limited access to eye care facilities. This kind of project seeks to reduce the barriers that traditionally limit access to the benefits of cataract surgery, such as the problem of how to identify those blind from cataract within a

target population and how to motivate them to undergo surgery, because there are different psychosocial and economic barriers that interfere in this decision process. It was found that fully one third of those for whom surgery was indicated refused the operation.

This program had different stages:

1. Identification of persons 50 years or older with visual impairment of 20/200 or worse in the better eye.

2. Ophthalmologic examination of those with the aforementioned visual limitation and identification of those with cataract.

3. Outpatient surgery performed by local surgeons at ophthalmologic centers near the target area.

4. Postsurgical follow-up in the patient's home.

5. Assessment of visual acuity after six months.

6. Maintenance of the reduction of cataract blindness obtained by the program, trying to control the incidence (new cases).

In Campinas, 319 patients met the visual criteria in stage 1. In Chimbote, the number of patients who met this criteria was 416. Comparing Campinas to Chimbote, 72 and 154, respectively, had operable cataracts; 48 of 72, compared with 86 of 154, agreed to surgery. At the three-week follow-up examination, in Campinas, 21 patients of 48 (45.2%) and in Chimbote, 43 patients of 86 (51.2%) had visual acuity corrected to 20/50 or better. In Campinas, 12 patients of 48 (25%) and in Chimbote, 12 patients of 86 (14%) had visual acuity of 20/200 or worse because of coexisting macular degeneration or diabetic retinopathy not detectable before surgery. In Campinas, of an operable cataract backlog of 72 patients, 48 had surgery. In Chimbote, of an operable cataract backlog of 154 patients, 86 had surgery. In both locations, a reduction of approximately 60% of

the backlog of cataracts was obtained. Data for follow-up six months after surgery are incomplete.

Some valuable aspects of this program that have interested ophthalmologists of different Latin American countries include the following:

1. The voluntary participation of the organized community in the different steps of the program (house-to-house survey, self-screening, mass media campaigns), motivation of the patient, and transportation to the ophthalmologic center and place of surgery, as well as postoperative follow-up in the patient's home.

2. Advantages of outpatient surgery that was not previously widespread in our population and its use in intensive surgical campaigns.

3. Acceptance by the community of this kind of health care.

4. Motivation of the local ophthalmologists to become more actively involved in a program of community eye care.

At this time, there are ten ongoing projects in nine Latin American countries. Their success depends on the economic support they need to obtain for their initial development. We are confident that this support will be the basis for their own future improvement and for the development of new programs. Additionally, this program looks for the best way to improve the efficiency of the infrastructure of ophthalmologic services in order to reduce costs. This program of the Pan-American Association of Ophthalmology has obtained two main achievements in Latin America: the successful treatment of blindness from cataract and the favorable change of attitude of ophthalmologists toward community service.

LETTERS TO THE JOURNAL

Botulinum Toxin Injections in the Treatment of Seventh Nerve Misdirection

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Misdirection of the seventh nerve occasionally occurs after regeneration of the nerve after paresis, which may be caused by such conditions as Bell's palsy. Many patients find that when they smile their eyelids narrow on the side of the seventh nerve misdirection and create a cosmetic deformity. Some of these patients can be adequately treated through a blepharoptosis procedure, such as the Fasanella-Servat procedure.[1] The Müller's muscle-conjunctival resection blepharoptosis procedure is effective in patients who preoperatively demonstrate a good response of their eyelid level and palpebral fissure both in the primary position of gaze and on smiling after instillation of 10% phenylephrine to the superior conjunctival fornix.[2]

There are patients, however, whose upper eyelids elevate to a cosmetically unacceptable high level in the primary position of gaze on instillation of phenylephrine even though they may have an acceptable appearance when they smile. In this group of patients, there has not been a procedure to correct the eyelid deformity fully on smiling without causing a retracted eyelid without smiling. I treated a patient who had seventh nerve misdirection whose upper eyelid elevated too high with 10% phenylephrine by injection of botulinum toxin.

A 28-year-old woman had Bell's palsy, which had affected her right side ten years previously. The patient continued to be bothered by the narrowing of her right eye when she smiled. In the primary position of gaze, her palpebral fissure width measured 9.0 mm on each side. When she smiled, the right palpebral fissure narrowed to 5.5 mm (Fig. 1).

On instillation of 10% phenylephrine to the right upper fornix, the right upper eyelid retracted to a level 2.0 mm higher than the left upper eyelid. When the patient smiled after phenylephrine instillation, her upper eyelid levels were symmetric. A blepharoptosis procedure in the right upper eyelid was contraindicated because of the probability that the upper eyelid would have cosmetically unacceptable retraction when the patient was not smiling.

Botulinum A toxin (0.1 ml of 2.5 units per 0.1 mm of solution) was injected into the right cheek and five sites of the right upper and lower eyelids. The sites injected were the temporal and nasal ends of the right upper eyelid, the temporal and central positions of the right lower eyelid, and the temporal right inferior orbital rim.

Postoperatively, the palpebral fissure width measured 9.0 mm on the right side and 9.5 mm on the left. There was no change on smiling (Fig. 2). For three months postoperatively the

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Fig. 1 (Putterman). Preoperative photograph of patient with seventh nerve misdirection leading to a narrow palpebral fissure of the right eye when she smiles.

Fig. 2 (Putterman). The patient after injection of botulinum toxin into the right upper and lower eyelids, with normal palpebral fissures apparent on smiling.

patient has instilled artificial tears four times a day and has no corneal staining or ocular irritation. She has not required additional botulinum injections but will probably need injections on a four- to eight-month basis, depending on how quickly the effects of the neurotoxin wear off.

Botulinum toxin injection appears to be an effective alternative treatment of seventh nerve misdirection in patients whose upper eyelids are not blepharoptotic in the primary position of gaze and in whom a blepharoptosis procedure is contraindicated. More patients must be treated to document this hypothesis.

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A Corneal Complication of Indirect Ophthalmic Laser Delivery Systems

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The recent development of a laser delivery system interfaced with the indirect ophthalmoscope has introduced a powerful new tool for photocoagulation of the fundus and retinal periphery. This instrument will become more commonly used as clinicians become familiar with its applications. The following case, however, illustrates a serious potential complication from the use of this instrument.

A partial expulsive choroidal hemorrhage occurred in a 67-year-old woman during a planned extracapsular cataract extraction. The cataract surgery was aborted and no lens was implanted. Her ocular history was remarkable only for successful cataract extraction with posterior chamber intraocular lens implantation in her fellow eye. She was referred to a retinal surgeon who performed a pars plana vitrectomy nine days after the initial operation, with fluid-gas exchange and drainage of suprachoroidal blood. Postoperatively, the patient did well with only minimal corneal edema. Small peripheral retinal tears then developed and an attempt was made to treat these with an indirect laser delivery system. Burn duration was 0.2 second and burn intensity was 120 mW. Buffered saline solution was used for corneal irrigation.

While performing this procedure in a darkened room, the retinal surgeon noticed a rapid worsening of his ability to visualize the fundus. The procedure was terminated and the lights in the room were turned on. Slit-lamp examination disclosed numerous discrete circular corneal opacities consistent with thermal burns involving all layers of the cornea.

These corneal opacities resolved somewhat
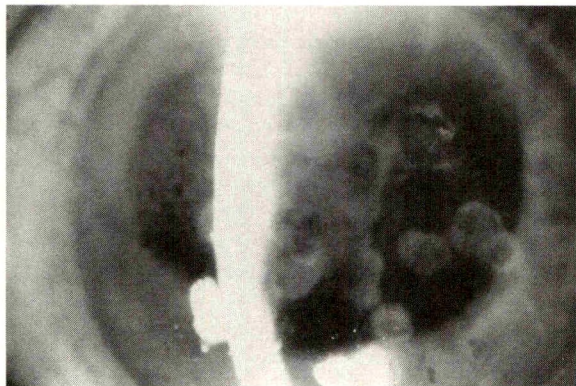
Fig. 1 (Rubinfeld, Pilkerton, and Zimmerman). Appearance of cornea four weeks after indirect laser treatment showing dense panstromal burns and corneal edema.
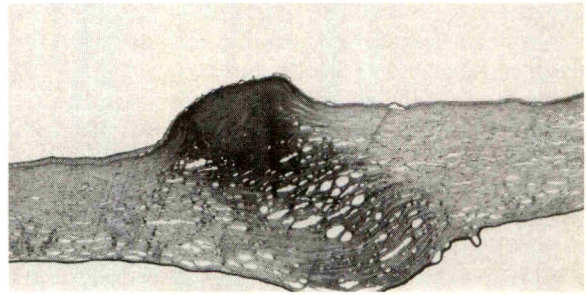
Fig. 2 (Rubinfeld, Pilkerton, and Zimmerman). The dark (deeply eosinophilic) lesion that markedly thickens the corneal stroma is a broad area of advanced coagulative necrosis involving the full thickness of the cornea. Keratocytes have vanished and the corneal lamellae are fused into a homogeneous mass, especially in the outer third of the lesion (hematoxylin and eosin, × 100).

over the course of four weeks. A retinal detachment was discovered on ultrasound examination, however, and the patient was referred for corneal consultation. On slit-lamp examination, four weeks after the laser procedure, approximately 12 1 × 1-mm dense off-white panstromal opacities were visible. The cornea was edematous with Descemet's folds visible, radiating out from each lesion (Fig. 1). The corneal opacities and edema precluded visualization of the fundus.

A penetrating keratoplasty, placement of a Landers-Foulks type 2 temporary keratoprosthesis, pars plana vitrectomy, fluid-gas exchange, retinotomy, endodiathermy, and a scleral buckling procedure were performed. The corneal button was sent for pathologic study (Fig. 2). Despite these efforts, untreatable proliferative vitreoretinopathy and traction retinal detachment resulted.

Corneal burns were a well-recognized complication associated with use of the xenon arc photocoagulator,[1] and early argon laser treatment.[2] With the development of contact lenses for delivery of laser energy to the anterior and posterior segments of the eye, the incidence of corneal burns as a complication of ophthalmic photocoagulation decreased dramatically, although several recent cases have been reported.[3]

One factor, which apparently predisposes the new laser delivery systems to produce corneal burns, stems from the use of these devices in a darkened room. During use of the indirect ophthalmoscope the eye as a whole is not visualized. These devices are designed rather to visualize the fundus. During movement of the

patient's eye and the surgeon's hand, laser energy can therefore be accidentally focused far from the desired target tissue.

We hope this report will alert retinal surgeons to the possibility of this potentially serious complication of the new hand-held laser delivery systems. Further modifications of these systems may decrease the likelihood of corneal damage in this manner. Previous studies on avoiding corneal laser burns have emphasized the importance of short burn duration, lower power settings, as well as maximizing beam size at the retina.[2] Continuous cool saline irrigation, long intervals between laser applications,[4] and hydrophilic bandage contact lenses[5] have also been proposed.

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The Use of Ureter Stone Forceps to Remove a Large Intraocular Foreign Body

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A variety of forceps have been developed to remove intraocular foreign bodies.[1-3] We encountered a large, dome-shaped, glass intraoc-
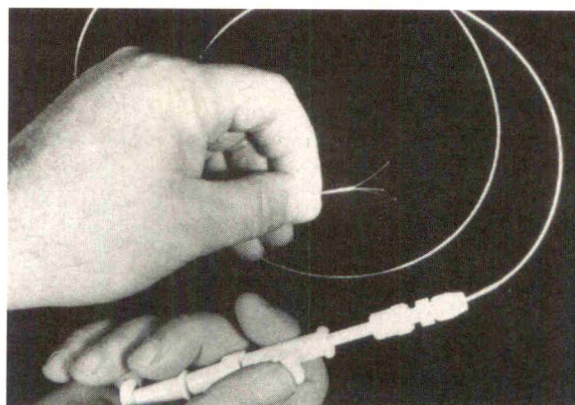
Fig. 1 (McCarthy, Pulido, and Soukup). Ureter stone extractor forceps in the open position.

ular foreign body that had smooth tapered edges making it difficult to grasp with diamond-tipped forceps. A readily available renal stone extractor (Fig. 1) was inserted through a standard vitrectomy port. This instrument easily and securely grasped the foreign body and brought it into the anterior chamber where it was removed through a limbal incision.

A 36-year-old man was watching his son shoot a BB gun when the gun discharged inadvertently. The pellet struck the right lens of the subject's spectacles, which dislodged a disk of glass that measured 10.5×11.0 mm in length and 3.5 mm in width from the posterior surface of the spectacle lens (Fig. 2). The glass entered the globe 8.0 mm from the corneoscleral limbus, producing a 12-mm vertical scleral laceration involving the lateral rectus muscle insertion. Visual acuity was R.E.: hand motions at 6 inches. A 1.4–log unit relative afferent pupillary defect was noted. A large vitreous hemorrhage precluded a view of the fundus. Orbital radiographs disclosed a large intraocular foreign body with no evidence of a pellet in the orbit.

A standard pars plana lensectomy and vitrectomy were performed. After removal of the vitreous hemorrhage, the foreign body was identified; it was lying flat on the inferotemporal retina. A large temporal retinal tear was evident at the entry site with a temporal retinal detachment, and a small tear was noted in the macula. Multiple attempts to grasp the foreign body with diamond-tipped forceps and elevate it into the anterior chamber were unsuccessful because the smooth, finely tapered edge of the foreign body would slip out of the forceps.

Ureter stone extractor forceps (Van-Tech, Inc., Spencer, Indiana) were then inserted through the pars plana with a light pipe provid-
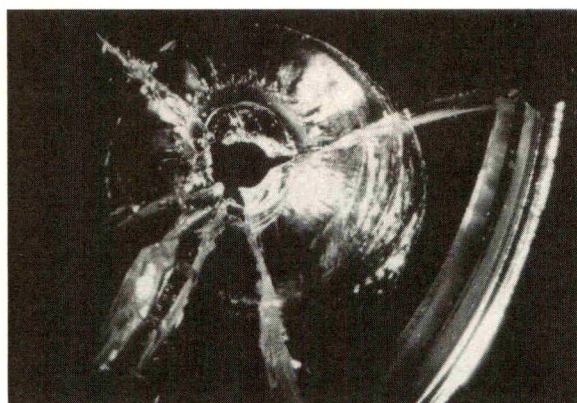
Fig. 2 (McCarthy, Pulido, and Soukup). Damaged spectacle lens of patient showing a large disk of glass dislodged from posterior surface.

ing illumination. The forceps were partly opened in the eye and the foreign body was tilted slightly, which enabled two of the prongs to extend beneath it while another prong remained anterior to the foreign body. The assistant then retracted the prongs, which allowed the foreign body to be firmly grasped and removed through a limbal incision. Argon green endolaser photocoagulation was applied around the retinal tears. An air-fluid exchange was performed, and C_3F_8 gas was injected into the eye. In the first two postoperative months the retina has remained attached. The patient has subsequently been lost to follow-up.

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A New Infusion Cannula for Advanced Proliferative Vitreoretinopathy

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Proliferative vitreoretinopathy is a major cause of failure in retinal reattachment surgery. The anterior component of proliferative vitreoretinopathy often involves cellular proliferation in the region of the vitreous base and the separated posterior hyaloid.[1] The resulting anterior vitreous traction often pulls the retina anteriorly. In severe cases, the peripheral retina is pulled forward over the pars plana and even up onto the posterior surface of the iris.

Successful treatment of this condition requires surgical release of this vitreoretinal traction.[1,2] Although it is desirable to use a standard, three-port vitreous surgery technique when possible, the anteriorly displaced retina often causes a problem.[3] Entry into the vitreous cavity through a sclerotomy site in the pars plana may create new retinal tears. It would be desirable to carry out the vitrectomy without the use of vitreous instruments, such as the infusion cannula, perforating this anteriorly displaced retina at any time during the procedure.

To avoid the damage to the displaced retina, a new infusion cannula has been designed (Fig. 1). This cannula is placed at the corneoscleral limbus through a standard microvitreoretinal knife incision. The cannula enters the eye parallel to the iris. It is then angled posteriorly at the
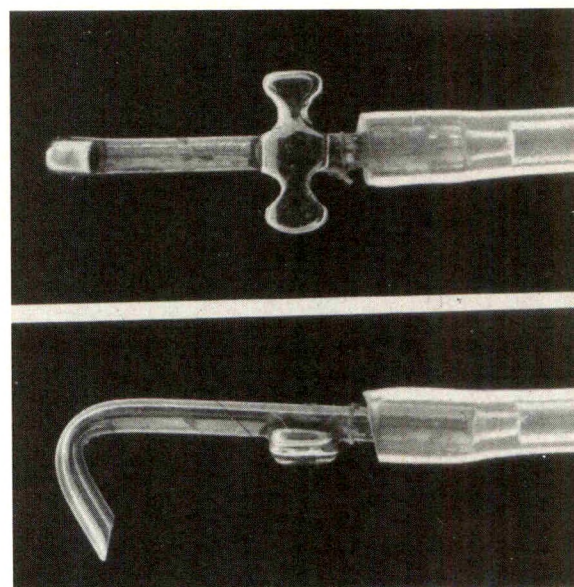
Fig. 1 (Landers, Semple, and Morse). View of infusion cannula from below (top) and side (bottom). Note base for positioning on sclera with mattress suture.
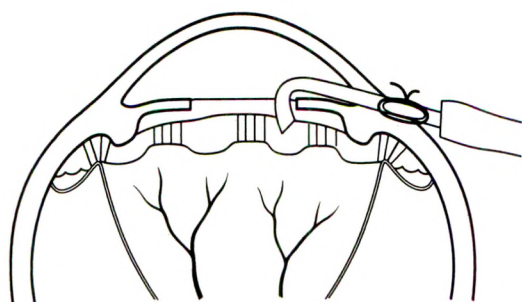
Fig. 2 (Landers, Semple, and Morse). Infusion cannula in position showing its relationship to anterior structures.

pupillary margin so that the flow of infusion fluid is downward into the vitreous cavity of the aphakic eye and, hence, away from the corneal endothelium (Fig. 2). The infusion cannula can be sewn onto the sclera in a manner similar to that of a standard pars plana infusion cannula. It is thus possible to approach the vitreous base with a minimal chance of the infusion cannula creating new retinal tears. We have used this infusion cannula successfully on several patients who had severe proliferative vitreoretinopathy and in trauma patients who have dense vitreous hemorrhage and preoperative ultrasonic evidence of a retinal detachment.

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Optic Disk Neovascularization in Juvenile Rheumatoid Arthritis

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Juvenile rheumatoid arthritis is a chronic, progressive disease that occurs during childhood. The most common ocular manifestation of juvenile rheumatoid arthritis is iridocyclitis. Other ocular manifestations include cataract, secondary glaucoma, and band keratopathy, which are related to chronic iridocyclitis.[1] Patients with ocular involvement generally have the pauciarticular disease and lack the systemic manifestations, lymphadenopathy, and fever. The patients with ocular involvement have a negative rheumatoid factor, but 80% of the patients have a positive antinuclear antibody titer associated with the disease.[2] We report a patient with juvenile pauciarticular rheumatoid arthritis who developed optic disk neovascularization.

A 4-year-old girl had juvenile rheumatoid arthritis. The patient's condition had been initially diagnosed by her pediatrician two years previously, when she had arthritis of her left wrist and right knee. An antinuclear antibody titer was performed and found to be positive. In the same year, she developed bilateral anterior uveitis, which required long-term topical corticosteroid therapy in both eyes to control the inflammation. The arthritis was controlled by oral prednisone. Minimal inflammation persisted over the next two years, and visual acuity remained 20/30 in each eye.

At 3½ years of age, the patient was referred to our institution in March 1989 when visual acuity began to deteriorate because of bilateral progressive cataracts in both eyes that were secondary to chronic inflammation and long-term topical corticosteroid therapy. Visual acuity was R.E.: 20/400 and L.E.: hand motions. The results of an anterior segment examination disclosed nasal band keratopathy in the right eye and a clear cornea in the left eye. There were trace cells and mild flare in the right eye and trace cells and no flare in the left eye. Extensive posterior synechiae were seen in the right eye. Intraocular pressure was R.E.: 11 mm Hg and L.E.: 18 mm Hg. A severe cortical cataract was noted in the right eye and a dense, white cataract was noted in the left eye. The patient had a red reflex in the right eye and no red reflex in the left eye.

The patient's cataract was removed by using a vitrectomy instrument in the left eye on March 21, 1989, and in the right eye on June 6, 1989. The entire lens capsule was removed during
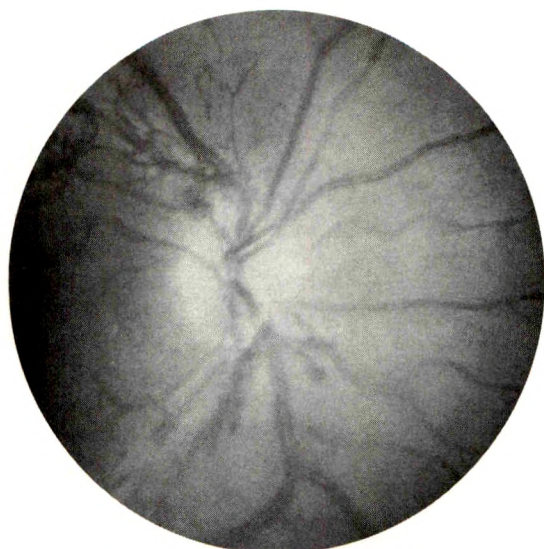
Fig. 1 (Semple, Landers, and Morse). Fundus photograph of optic nerve head neovascularization in the right eye, July 31, 1989.
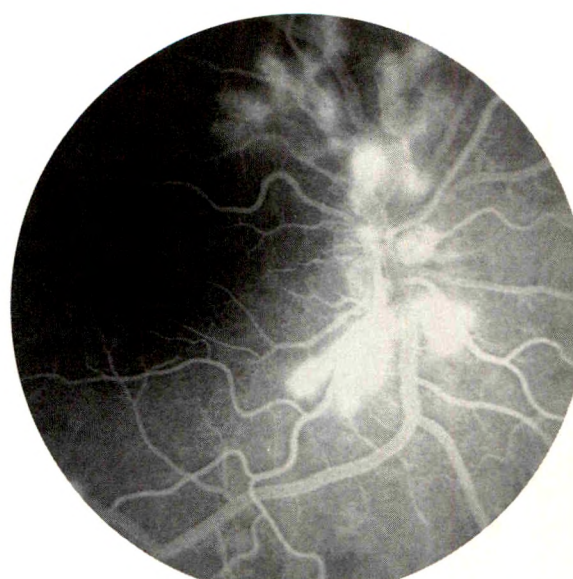
Fig. 2 (Semple, Landers, and Morse). Transit phase of intravenous fluorescein angiogram of right eye, which confirms extensive neovascularization of the optic nerve head, August 1989.

both procedures. Seven weeks later, visual acuity was R.E.: 20/200 and L.E.: 20/60. The results of an examination at this time disclosed no inflammation in the left eye and trace cell and flare in the right eye. The retina, disk, and vessels were normal in the left eye. The retina was attached in the right eye, but florid optic nerve head neovascularization was noted (Fig. 1). A fluorescein angiogram confirmed the neovascularization of the disk (Fig. 2). Capillary nonperfusion was not detected, and cystoid macular edema was seen in the late phase of the angiogram. The patient was given 1% prednisolone acetate every three hours and 1% atropine twice daily in the right eye. A subtenon's injection of triamcinolone acetonide 20 mg was given in the right eye. Two months after subtenon's injection of triamcinolone acetonide, the optic disk neovascularization had regressed and visual acuity improved to R.E.: 20/80. A second subtenon's injection of triamcinolone acetonide 20 mg was given, and two months later the neovascularization had completely involuted and best-corrected visual acuity was R.E.: 20/50.

Iridocyclitis is the most common ocular complication of juvenile rheumatoid arthritis.[1,2] Although optic disk neovascularization is associated with chronic uveitis, most cases of uveitis with optic disk neovascularization, retinal neovascularization, or both have associated vasculitis and ischemia as the possible cause of the neovascularization. There are several pub-

lished reports associating optic disk neovascularization alone with posterior uveitis without associated capillary nonperfusion noted on fluorescein angiogram.[3-5] Most of these cases were diagnosed as chronic cyclitis and none had documented juvenile rheumatoid arthritis.

The treatment of the optic disk neovascularization in this patient was based on the resolution of the chronic inflammation. Neovascularization associated with posterior uveitis has been treated with either panretinal photocoagulation, corticosteroid therapy, or both, although panretinal photocoagulation is probably of limited value in the absence of angiographic evidence of ischemia.[5]

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Complete Visual Recovery After *Bacillus cereus* Endophthalmitis in a Child

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Department of Ophthalmology, Mary Imogene Bassett Hospital (P.M.B., I.H.L.) and Hartford Hospital (A.J.P.). This study was presented at the annual meeting of the Vitreous Society, Orlando, Florida, December 9, 1989.

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Bacillus cereus endophthalmitis destroys vision rapidly and may lead to loss of the globe.[1,2] Diagnosis was made at an early stage in two patients in whom useful vision was preserved.[3,4] We treated a 3½-year-old boy who developed *Bacillus* endophthalmitis and had complete visual recovery.

A healthy boy was struck in his right eye by a manure fork and sustained a 6-mm horizontal corneal laceration, not involving the visual axis. The child was brought to the operating room within four hours of the injury. The corneal laceration was closed. No hypopyon was noted. A dense fibrinous membrane was peeled from the iris, which allowed excellent visualization of the fundus. Prominent retinal periphlebitis was noted in the superotemporal quadrant. The adjacent pars plana, contiguous with the limbal extent of the corneal laceration, was covered by white inflammatory material from the 1 o'clock to the 2 o'clock meridians. Two clumps of vitreal cells were seen overlying the inflamed pars plana. The remainder of the vitreous cavity was clear (Figure). Based on the finding of retinal periphlebitis, a diagnosis of endophthalmitis was suspected.

A pars plana sclerotomy was made in the area of maximal involvement and 0.2 ml of solid
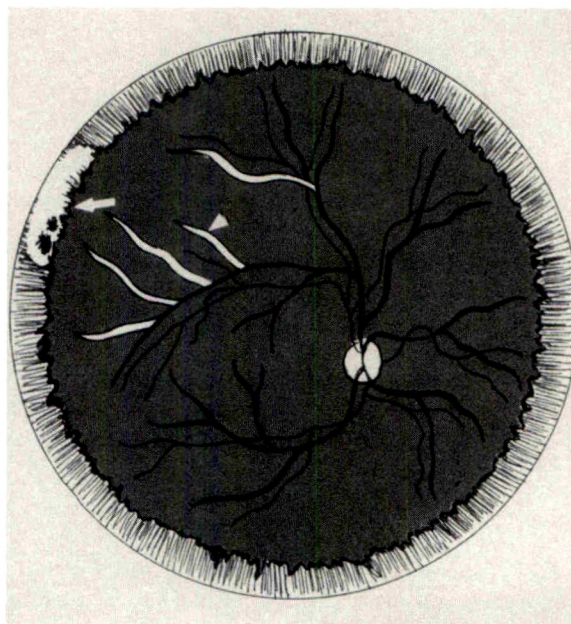
Figure (Beer, Ludwig, and Packer). Intraoperative fundus appearance. Striking periphlebitis (arrowhead) and snowbanking of pars plana with clumps of vitreous cells (arrow) was found in the quadrant contiguous with the corneal laceration.

vitreous was removed with the vitreous cutter and replaced with 1 mg of clindamycin and 200 µg of intravitreal gentamicin. Subconjunctival gentamicin 20 mg and cefazolin 40 mg were administered.

Vitreous cultures grew *B. cereus* and coagulase negative *Staphylococcus aureus*. Systemic ceftriaxone sodium and clindamycin were administered for 14 days. Clinically, the endophthalmitis resolved in the immediate postoperative period, as no hypopyon or vitreous clouding developed.

Patching of the left eye was begun on the ninth postoperative day. A posterior subcapsular cataract developed and was removed 24 days after the original injury. Prompt refractive correction was provided by using a silicone contact lens and aphakic spectacle correction with patching while lens wear time was being accumulated. Full-time contact lens wear was achieved six weeks after the injury, and bifocal spectacles were then prescribed. Patching was tapered to one hour daily. Twelve months after injury, visual acuity measured 20/30 in each eye (illiterate E), 30-second stereopsis was present, and ocular alignment was normal.

The success in this patient was because of

unusually early diagnosis and treatment (six hours after the injury). Retinal periphlebitis has been documented as an early sign of endophthalmitis.[5] It precedes vitreous clouding or even hypopyon formation. The prompt use of appropriate intraocular antibiotics limited exotoxin production and allowed the vitreous cavity to remain clear. Prolonged vitreous clouding, which is common after endophthalmitis, could have caused significant deprivational amblyopia.

The early use of refractive correction and amblyopia therapy contributed to the excellent functional result. The critical period during which loss of stereopsis becomes irreversible despite reversibility of deprivational amblyopia in childhood traumatic cataracts is unknown. In our experience it has occurred with an amblyopia treatment delay of as little as one month in a patient who was 3½ years of age.

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Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

A Systemic Approach to the Diagnosis of Chronic Conjunctivitis

EDITOR:

In the article "A systematic approach to the diagnosis of chronic conjunctivitis" by P. A. Rapoza, T. C. Quinn, A. C. Terry, J. D. Gottsch, L. A. Kiessling, and H. R. Taylor (Am. J. Ophthalmol. 109:138, February 1990), the authors have encouraged ophthalmologists to examine their patients who have chronic conjunctivitis systematically and thoroughly. This can only, in the long term, benefit patients with such disorders.

The authors provide the following criteria for entry into the study: conjunctival injection, discharge, or both occurring for more than two weeks. Conjunctivitis implies an inflammatory process of the conjunctival ocular surface, and I believe certainly deserves a tight definition. Further, it was not certain in the Patients and Methods section whether any patients had been treated before their examination in the special chronic conjunctivitis clinic. Patients with conjunctivitis secondary to blepharitis, dry eye, or lacrimal excretory problems were excluded. The authors mention later in the Patients and Methods section, however, that all of their patients were assessed for a dry eye syndrome. It would seem to me that patients with chronic conjunctivitis should be assessed as a composite group, since the disorders the authors have excluded, such as blepharitis and dry eye syndromes, can indeed predispose the eye to bacterial infection and may contribute to a microbiologic diagnosis when assessed. Smolin[1] recommended this previously. In any ocular surface disease, it is also vital to assess the adequacy of blinking and any evidence of definite or presumed nocturnal lagophthalmos. In 1984, Loughhead and I[2] showed that 5% of the population may have presumed nocturnal lagophthalmos, and we hypothesized that lagophthalmos and the patient's Bell's phenomenon should also be assessed in any patient with a syndrome resembling chronic conjunctivitis.

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———————— **Reply** ————————

EDITOR:

We appreciate the comments of Dr. Francis regarding our study. The definition of a disease entity is a construct designed to assist medical personnel in categorizing patients with similar disorders, which enables generalization for treatment decisions. Our definition of chronic conjunctivitis was developed to collect a population of patients with primary, not secondary, conjunctivitis. Therefore, conjunctivitis secondary to blepharitis and dry eyes was specifically excluded. Because of the ubiquitous nature of dry eyes and our special interest in those disorders, assessment of dry eyes was repeated despite previous examination by physicians who referred patients for inclusion in our study.

Dr. Francis appropriately emphasizes examining patients for lagophthalmos as a cause of chronic conjunctivitis. We routinely include this in our examinations and regret not specifically mentioning it in our article. Finally, patients who were previously treated for conjunctivitis were enrolled in our study but all treatment was withheld for at least 24 hours before the examination.

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BOOK REVIEWS
Edited by H. Stanley Thompson, M.D.

New Methods of Sensory Visual Testing. Edited by Michael Wall and Alfredo A. Sadun. New York, Springer-Verlag, 1989. 137 pages, index, illustrated. $49.95

Reviewed by JOEL M. WEINSTEIN
Madison, Wisconsin

Clinicians are becoming increasingly aware of the limitations of some of the old reliable tests of visual sensory function. Snellen visual acuity and kinetic perimetry are unable to detect and characterize many of the abnormalities in patients with optic nerve and retinal disease. The inadequacy of these tests becomes obvious when one considers that as many as 40% of the axons in the optic nerve may be lost in patients with normal Snellen visual acuity and kinetic perimetry. At the same time, improvements in therapy make it imperative that damage to the visual system be detected in its earliest stages. A number of newer testing methods, such as contrast sensitivity function, have been derived from basic laboratory investigation and are now in limited clinical use. The aim of this book, which is fulfilled admirably, is to outline the physiologic basis of some of these newer testing procedures and to "acquaint clinical and research ophthalmologists with the proper interpretation of test results and emphasize the advantages and utility of each test."

The text is valuable from both a practical and an academic point of view. It begins with a short, clear chapter on a complex topic: "Parallel Processing in the Human Visual System." This is followed by six chapters, each by a different author, covering brightness testing, critical flicker fusion frequency, contrast sensitivity testing, clinical electrophysiology, examination of the 10 degrees of visual field surrounding fixation, and automated perimetry. The physiologic basis of each test is fully explained, and the appropriate applications for each are well documented. Each of the chapters can be read alone as a detailed review of the subject. The chapter, "Examination of the Ten Degrees of Visual Field Surrounding Fixation," is a good example of the practical value of the book. Six standard tests that have been used for evaluation of central visual function are compared. These include threshold Amsler grid, static tangent screen, automated threshold perimetry with a 2-degree central grid, automated threshold perimetry with a 6-degree grid, kinetic tangent screen, and standard Amsler grid testing. As presented, the superiority of threshold Amsler grid testing is convincing.

The text is a valuable addition to the library of both clinical and research ophthalmologists. Reading the book will improve the treatment of patients with such diverse problems as mild paracentral visual loss, opaque media, and functional visual loss. Although a few of the tests described in the book, such as pattern electroretinography, are not yet in everyday clinical use, refinements of these procedures will certainly be in widespread use in the near future, and clinicians will certainly benefit from knowing about them. The brief foreword by Harry Quigley, M.D., contains an interesting historical perspective on the development of new tests of visual function and is well worth reading.

Neuro-Ophthalmology, ed. 2. Edited by Joel S. Glaser. Philadelphia, J. B. Lippincott, 1990. 557 pages, index, illustrated. $75

Reviewed by JOHN W. GITTINGER, JR.
Worcester, Massachusetts

In 1977 when I finished my neuro-ophthalmology fellowship and joined the ranks of junior faculty, one of the more useful books on my shelf was the then recently published first edition of Glaser's Neuro-Ophthalmology. Glaser was usually the best source, short of going to the library and slogging through the Index Medicus, for a current reference. Walsh and Hoyt provided the in-depth background, and Glaser brought the topic up to date.

The second edition is longer by 200 pages and has 13 collaborators rather than three, but the text still stands ready to do the same for its readers. Using the format of Duane's Clinical Ophthalmology, of which they are a part, these 17 chapters cover most of the important, and a

few not so important, topics in neuro-ophthalmology. Chapters on history and examination are followed by a review of visual system anatomy. Three chapters cover topical diagnosis of the afferent visual system. May and Galetta provide a comprehensive discussion of the facial nerve and its disorders. Three chapters on ocular movements follow. The sophistication of ocular motor system analysis by Daroff, Dell'Osso, Troost, and Leigh is implicitly acknowledged by an appended glossary. The final six chapters offer an overview of the current and classic literature on infranuclear and neuromuscular ophthalmoplegia, orbital disease, the pupil, migraine, and vascular malformations.

Dr. Glaser is not afraid to express his opinions, which occasionally differ from mine and perhaps those of other neuro-ophthalmologists. He prefers the description, "hyaline bodies of optic nerve," to optic disk drusen, with the consequence that the latter are not indexed. He considers retrobulbar depot corticosteroid injection on the involved side "a reasonable procedure" for the treatment of arteritic anterior ischemic optic neuropathy. I would like to see the evidence that this is effective before recommending it for general use, especially since Glaser advocates that therapy "not be delayed for results of erythrocyte sedimentation rate or biopsy." In terms of emphasis, functional visual loss, which constitutes a large portion of my neuro-ophthalmic practice, receives short shrift.

Setting aside these minor limitations, I recommend this book to neurology residents for their libraries. Ophthalmology residents will probably want to purchase the entire five volumes of Duane. The vigorous writing, the copious illustrations, and the expertise of the authors all combine to make this the best available one-volume text of neuro-ophthalmology.

rather than disease entities, which is an interesting approach to the clinical and surgical management of eyelid and orbital problems. The five major sections are Osteology, Nose and Paranasal Sinuses, Lacrimal Excretory System, Eyelids, and Orbits. Each chapter begins with a clinical review of the topic, followed by pertinent anatomy, important abnormalities, and selected surgical procedures. As stated in the Preface, this text is intended for the surgeon planning the surgical approach, the clinician, the resident, and the medical student.

The photographs, gross dissections, and illustrations are the great strengths of this atlas. There are numerous illustrative, black and white, clinical photographs accompanying well-done, clear, and accurate line drawings. They all help to emphasize the text. Supplementing these figures are superb photographs of cadaver dissections that demonstrate the gross anatomy described.

This surgical atlas clarifies complex surgical procedures by using the gross anatomy as a basis for understanding. The scope of this book does not allow any discussion of the histologic aspects of the disease entities and virtually none are included. This text will be best used in conjunction with a basic oculoplastics textbook.

Its greatest drawback is the shortage of reference citations. I would like to have easy access to specific references while reading each chapter. There is, however, an extensive bibliography at the end of each section.

This text should be thought of as an adjunct reference work on eyelid or orbital disorders. The chapter, "Clinical Considerations," though comprehensive, is brief, and little discussion of inevitable complications of the surgical procedures is included. The text is an excellent atlas to complement a basic textbook.

Surgery of the Eyelids and Orbit. An Anatomical Approach. By Bradley N. Lemke and Robert C. Della Rocca. Norwalk, Connecticut, Appleton & Lange, 1990. 332 pages, index, illustrated. $150

Reviewed by CHRISTINE C. NELSON
Ann Arbor, Michigan

The text of this combined atlas and textbook is organized according to anatomic divisions

Ophthalmic Lasers. A Second Generation. Edited by Wayne F. March. Thorofare, Slack Inc., 1990. 363 pages, index, illustrated. $90

Reviewed by RICHARD K. PARRISH II
Miami, Florida

Wayne March has assembled an impressive group of authors for this book. The approaches to the subjects are as varied as the individual personalities. The chapter by Charles Townes, "The Development of Laser," contains great

personal insight into the development of the first laser that originated as an offshoot of his investigation at Bell Telephone Laboratory. Similarly, the chapters by Gerd Meyer-Schwickerath, "The Development of Photocoagulation" and "Xenon Photocoagulation of Tumors," are filled with vignettes of the early trying times of photocoagulation.

The text consists mainly of clinical impressions and indications for the use of dye, argon, krypton, excimer, YAG, and carbon dioxide lasers. "The Development of Laser Trabeculoplasty," by David Worthen and David Wickham, relates the trials and tribulations of early laser treatment of the angle. The chapter has the tone of a transcript of a friendly chat with David Worthen, and it reminds us how sorely his friendship and wisdom are missed.

"YAG Laser Contact Lens Theory," by Hanspeter Loertscher and Franz Fankhauser, describes the use of the contact lens on a more mathematical basis than most ophthalmologists are accustomed to and will probably be beyond the interests of many. Stephen Trokel's section, "Regulatory and Safety Considerations of the YAG," offers a review of the risks and benefits of laser treatment, more detailed than Food and Drug Administration or safety regulations. Specifically, the question of whether protective spectacles should be worn by surgeons, assistants, and observers is not addressed.

Two extremely detailed chapters outline the management of laser treatment and specific retinal conditions. "An Approach to Laser Management of Diabetic Retinopathy," by Stevens and associates, is a precise, current review of the indications for panretinal photocoagulation and for focal laser treatment for patients with diabetic retinopathy. It contains a brilliantly organized algorithm of the indications of various laser treatments for different stages of diabetic retinopathy. "Present Indications and Future Promise of Krypton Laser," by J. Donald M. Gass, spans some 36 pages, approximately one tenth of the book, and has detailed case histories illustrating the advantages of krypton laser over argon laser for photocoagulation within the capillary-free zone.

Laser treatments for patients with glaucoma are described in Chapter 4, "Current Use of the Dye Laser," by Wayne March (YAG laser internal sclerostomies) and Chapter 8, "Corneal Photoablation," by Michael Berlin (excimer laser photocoagulation). Although it would be more convenient to have filtration surgical procedures in one chapter, both discussions were easily located in the well-organized index. A

glossary is included that, although limited, serves·as a starting point for the laser novice.

This text is a quick refresher for the practicing ophthalmologist and an update on current laser needs. The book will also be of value for ophthalmology residents who seek a broad overview of laser intervention. I found the chapters that reveal the human soul behind the early laser developments of Schwickerath, Worthen, Townes, and Gass to be the most enjoyable.

Surgical Intervention in Corneal and External Disease. By Richard L. Abbott. San Francisco, Continuing Ophthalmic Video Education Committee of the American Academy of Ophthalmology, 1990. Videotape

Reviewed by PETER GLOOR
Iowa City, Iowa

This videotape is on the surgical management of a variety of corneal and external disorders. It lists medical and surgical treatment options for common conditions and illustrates Dr. Abbott's approaches to the surgical procedures.

Procedures covered include cryosurgery of trichiasis, tarsorrhaphy for corneal exposure, punctal occlusion for dry eyes, stromal puncture for recurrent epithelial defects, conjunctival flap for persistent epithelial defects, gluing of small corneal perforations, cautery of Bowman's layer for painful bullous keratopathy, and conjunctival transplant in pterygium excision. Penetrating keratoplasty is not discussed.

With so many procedures covered in a half-hour tape, the indications, techniques, and complications are not reviewed in detail. Yet, the important points are covered, and a judicious ophthalmologist could perform many of the procedures described by using the instructions from this videotape alone.

Dr. Abbott's approach to the treatment of corneal and external disorders is practical. The procedures he describes are effective, and most can be performed in the office without special equipment.

There are some useful treatment options that are not explored in this tape. For example, in the evaluation of dry eyes, Dr. Abbott illustrates two methods of temporarily occluding puncta with a suture but only mentions silicone punctal plugs briefly. The use of silicone plugs

is helpful in many situations since the plugs may be left in place permanently and constitute not only an aid in the evaluation of dry eyes but, at the same time, a reversible treatment for the condition.

This videotape arms the ophthalmologist with practical surgical alternatives when medical therapy fails in the treatment of a variety of common corneal and external ocular disorders.

Pernkopf Anatomy. Atlas of Topographic and Applied Human Anatomy, vol. 1. Head and Neck. Edited by Werner Platzer. Baltimore, Urban & Schwarzenberg, 1989. 372 pages, index, illustrated. $175

Reviewed by THOMAS A. WEINGEIST
Iowa City, Iowa

This text has been a classic for more than 40 years. The third edition has been edited by Werner Platzer, who was Pernkopf's prosector and colleague; it establishes a new and still higher standard of quality. Most of the original illustrations have been retained and new ones have been added. The original Latin leaders have been completely replaced by contemporary English terms. The editor chose to omit all the radiographs to avoid make the volume unmanageable. This is a loss, but a wise decision, given the advances in imaging technology that have occurred in recent years.

Students of anatomy, and physicians and surgeons interested in knowing the finest nuances of the anatomy of the head and neck will find this atlas to be an invaluable resource. The illustrations are unsurpassed in their clarity and meticulous attention to detail.

the following topics: cornea (seven), anterior chamber (four), retina (six), phototoxicity (four), and side effects (eight).

Practice Made Perfect. The Physician's Guide to Communication and Marketing. By Edna Kaplan. Boston, Barrington Press, 1990. 261 pages, index. $39.95

Here is advice for physicians, which describes how to assess ones' practice, build patient trust, streamline the office, improve efficiency, make the staff an asset, find ways to serve the community, prepare for media appearances, and the like.

Wills Eye Hospital. Office and Emergency Room Diagnosis and Treatment of Eye Disease. Edited by Mark A. Friedberg and Christopher J. Rapuano. Philadelphia, J. B. Lippincott, 1990. Softcover, 457 pages, index. $37.50

This text was put together by the entire second-year Wills ophthalmology residents in an effort to cut out the extra verbiage in ophthalmology and get right to the important facts. It opens with the differential diagnosis of common ocular symptoms and signs, followed by injury to the eye, and finally various areas of ophthalmology described in more detail. It is, naturally, presented in outline form for ready reference. The authors are to be commended for their energy and enterprise, and I hope, with them, that their book will become the dog-eared companion of every first-year ophthalmology resident and emergency room physician.

Books Received

Ocular Toxicology. Proceedings of the First Congress of the International Society of Ocular Toxicology. Edited by Sidney Lerman and Ramesh C. Tripathi. New York, Marcel Dekker, Inc., 1990. 420 pages, index, illustrated. $99.75

The symposium was held in Toronto in June 1988. Thirty-three papers were presented on

The Book List

Envisioning Information. By Edward R. Tufte. Cheshire, Connecticut, Graphics Press, 1990. 126 pages, index, illustrated. $48

Leaders in Ophthalmology in the Asia-Pacific. Edited by Lim Kuang Hui. Lower Kent Ridge Road, Singapore, XXVI International Congress of Ophthalmology, 1990. 280 pages, illustrated. (No price given)

Major Eye Centres of the World. Edited by Lim Kuang Hui and Arthur Lim Siew Ming. Lower Kent Ridge Road, Singapore, XXVI International Congress of Ophthalmology, 1990. 189 pages, illustrated. (No price given)

Technical Manual, ed. 10. Edited by Richard H. Walker. Arlington, Virginia, American Association of Blood Banks, 1990. 655 pages, index, illustrated. $33 (members), $40 (nonmembers)

World's Major Blinding Conditions. Edited by Arthur Lim Siew Ming. Lower Kent Ridge Road, Singapore, XXVI International Congress of Ophthalmology, 1990. 203 pages, illustrated. (No price given)

ABSTRACT DEPARTMENT

Acta Endocrinologica

Azathioprine in the treatment of thyroid-associated ophthalmopathy. Perros, P., Weightman, D. R., Crombie, A. L., and Kendall-Taylor, P. (Endocrine Unit., Dept. Med., Medical School, Univ. Newcastle upon Tyne, Newcastle upon Tyne, NE2 4HH, United Kingdom). Acta Endocrinol. 122:8, 1990.

Azathioprine is used in the treatment of thyroid-associated ophthalmopathy, but its effectiveness has not been evaluated. In the present study 20 patients with moderately severe ophthalmopathy were recruited; 10 patients received azathioprine and the other 10 matched patients served as controls. During the treatment period (lasting 1 year) and 1 year later, no changes were detected in exophthalmometer readings, visual acuity or measurement of palpebral aperture. Differential intraocular pressure fell with time in both groups. Azathioprine treatment did not significantly influence these parameters, although it did induce significant decrease in thyroid microsomal antibodies and in thyroid-stimulating hormone binding inhibiting immunoglobulin index. The study demonstrates that thyroid-associated ophthalmopathy of moderate severity, often improves with time without treatment. Azathioprine is not an effective treatment for patients with moderately severe thyroid-associated ophthalmopathy. The study emphasises the necessity for an adequately matched control population in the evaluation of therapy. (2 figures, 1 table, 15 references)—Authors' abstract

Archives of Otolaryngology—Head and Neck Surgery

Endoscopic transnasal orbital decompression. Kennedy, D. W., Goodstein, M. L., Miller, N. R., and Zinreich, S. J. (Dept. Otolaryngol. Head and Neck Surg., Johns Hopkins Hosp., 600 N. Wolfe St., Baltimore, MD 21205). Arch. Otolaryngol. Head Neck Surg. 116:275, 1990.

Orbital decompression for dysthyroid orbitopathy has traditionally been performed through either an external or a transantral approach. The advent of intranasal endoscopes allowed for the development of a transnasal approach for medial and inferior orbital wall decompression. Using this approach, orbital decompressions were performed on 13 orbits in eight patients with severe complicated dysthyroid orbitopathy. Simultaneous bilateral lateral orbitotomies were performed on five patients. Walsh-Ogura decompressions and lateral orbitotomies were performed on two orbits. When combined with lateral orbitotomy, Hertel measurements improved an average of 5.7 mm in orbits decompressed transnasally and 4.5 mm in orbits decompressed with a Walsh-Ogura approach. Transnasal decompression alone improved Hertel measurements an average of 4.7 mm. Visual acuity improved in three of four patients with optic neuropathy, and in all patients with exposure keratopathy. The authors conclude that the endoscopic transnasal approach provides comparable decompression to traditional methods while avoiding the morbidity of an external ethmoidectomy or Caldwell-Luc antrotomy. (8 figures, 2 tables, 31 references)—Authors' abstract

Graefe's Archive for Clinical and Experimental Ophthalmology

Recurrent Salzmann's corneal degeneration. Severin, M., and Kirchhof, B. (Universitäts-Augenklinik, Joseph-Stelzmann-Strass 9, D-5000 Köln 41, Federal Republic of Germany). Graefes Arch. Clin. Exp. Ophthalmol. 228:101, 1990.

Three keratoplasties were carried out on two patients because of nodular degeneration of the cornea. Progress after keratoplasty could be followed up in one eye for 17 months and in the other two eyes, for 2.5 and 9 years, respectively. The implant with the short follow-up of only 17 months remained glass-clear; nothing abnormal was discovered during the checkups. In the case of the other patient in whom a longer follow-up period was possible, the following findings were evident: (1) a remarkably late epithelial immune response in one eye (after 18

months) with subsequent incomplete reepithe-lisation and formation of fine, superficial, cloudy opacity (observation period 2.5 years); (2) formation of dense but flat, superficial areas of opacity in the cornea of the other eye (observation period 9 years). These areas may be regarded as a precursor of Salzmann's corneal degeneration. No difference could be found between the histological findings in the explants and those in a degenerative pannus or an older scar caused by inflammation of the Bowman membrane. (12 figures, 11 references)—Authors' abstract

International Journal of Radiation Oncology Biology, Physics

The results of radiotherapy for orbital pseudotumor. Lanciano, R., Fowble, B., Sergott, R. C., Atlas, S., Savino, P. J., Bosley, T. M., and Rubenstein, J. (Dept. Radiation Oncol., Fox Chase Cancer Ctr., 7701 Burholme Ave., Philadelphia, PA 19111). Int. J. Radiat. Oncol. Biol. Phys. 18:407, 1990.

Between January 1982 and March 1987, 23 patients (26 orbits) were treated for orbital pseudotumor with radiation therapy at the Department of Radiation Oncology, Hospital of the University of Pennsylvania. The patients were referred for clinical relapse after steroid taper in 70%, no response to steroids in 17%, and no steroid treatment (refused or contraindicated) in 13%. Presenting symptoms/signs included soft tissue swelling in 92% of orbits, pain in 92%, proptosis in 85%, and extraocular muscle dysfunction of ptosis in 69%. Decreased visual acuity was seen in only 19% of orbits. Biopsy was performed in nine patients. Treatment consisted of 2000 cGy in 2 weeks in 10 fractions for all patients. Median follow-up was 41 months, with a mean of 53 months, and a range of 21–92 months. Complete response was documented in 87% of orbits with soft tissue swelling, 82 with proptosis, 78% with extraocular muscle dysfunction, and 75% with pain. Of the five patients with visual acuity defects, three experienced complete recovery. There was no difference in complete response in patients biopsied versus those not biopsied. Overall, 17 orbits have remained in complete orbital response with no further steroid requirements (66%). Three orbits suffered local relapse at some point following radiation therapy and

were retreated with steroids. These three orbits had durable local control off steroid at last follow-up (11%). Therefore, 77% of orbits attained durable local control and were steroid independent with radiation therapy alone or radiation therapy followed by steroids for relapse. Only one patient developed systemic lymphoma with follow-up. No pretreatment clinical factor reached statistical significance with respect to prognosis following radiation therapy at the < .05 level. There were no significant acute or chronic side effects secondary to treatment. Steroids should continue to be first line treatment for orbital pseudotumor, but radiation has a well-defined role in cases of steroid failure or in patients unable to tolerate steroid therapy. (3 tables, 26 references)—Authors' abstract

International Ophthalmology

Antilens antibodies in cataract and inflammatory eye disease: an evaluation of a new technique. Patel, M., Shine, B., and Murray, P. I. (Dept. Pathology, Inst. Ophthalmol., 17-25 Cayton St., London EC1V 9 AT, England). Int. Ophthalmol. 14:97, 1990.

A new technique measuring serum antoantibodies to lens proteins, employing antigen linked to magnetisable cellulose particles and fluorescent end-point detection, was used to examine patients with senile cataract and inflammatory eye disease. 40% of patients with senile cataract had antibodies to lens proteins, as did 28% of patients with heterochromic cyclitis and 20% of patients with uveitis, while there were no positive sera from patients with scleritis. The single patient with lens-induced uveitis had a high titre, but so did some patients with senile cataract. With the incorporation of a standard curve this technique offers a reliable quantitative essay for lens autoantibodies. It may provide a valuable tool for the investigation of pathogenetic mechanisms in cataract and inflammatory eye disease. (1 figure, 26 references)—Authors' abstract

Proliferative vitreoretinopathy—is it anything more than wound healing at the wrong place? Weller, M., Wiedemann, P. and Heimann, K. (Univ. Eye Clin. Cologne, Joseph-Stelzmann-Strasse 9, 5000 Köln 41, West Germany). Int. Ophthalmol. 14:105, 1990.

Proliferative vitreoretinopathy is a reactive process of the ocular tissue after perforating trauma, retinal detachment, and surgical manipulations. Although several studies, most of them experimental, have focused on the detection of specific etiologic factors in the development of proliferative vitreoretinopathy, there is compelling evidence that proliferative vitreoretinopathy is nothing more than a physiologic tissue repair process with undesirable consequences for the retina. Important features of proliferative vitreoretinopathy involving the role of platelets, mononuclear phagocytes, and fibroblasts parallel the chain of events observed in tissue repair elsewhere in the body. Numerous experimental models for proliferative vitreoretinopathy, originally designed to find specific stimuli for the generation of intraocular traction membrane formation, have shown that the process of proliferative vitreoretinopathy is the common pathway of the eye's reaction to vitreoretinal trauma of any kind. Accordingly, vitreoretinal surgeons could learn a lot from the work of other disciplines, e.g. surgery and dermatology, on wound healing, and the factors known to modify wound healing elsewhere in the body should be taken into consideration. The well-established impairment of tissue repair processes caused by medical treatment with corticosteroids and cytotoxic agents suggests a combined medication approach to proliferative vitreoretinopathy as an adjunct to surgical treatment, using refined methods of application and dosage. Steroids and cytotoxic drugs will influence the course of proliferative vitreoretinopathy by suppressing macrophages recruitment and the initial inflammatory reaction as well as the proliferative phase of wound healing with traction retinal detachment, respectively. (2 tables, 125 references)—Authors' abstract

Xerophthalmia, keratomalacia and nutritional blindness. Sommer, A. (Data Ctr., Wilmer 120, Johns Hopkins Hosp., 600 N. Wolfe St., Baltimore, MD 21205). Int. Ophthalmol. 14:195, 1990.

Vitamin A deficiency remains a major cause of pediatric ocular morbidity. Over five million children develop xerophthalmia annually, a quarter million or more becoming blind. It is also a major pathway for measles-associated blindness, particularly in Africa. Treatment is practical and inexpensive, based upon the oral administration of 200,000 IU vitamin A on two successive days, at a cost of 10 cents U.S. Given the potential rapidity of corneal necrosis (keratomalacia) and the relative inaccessibility of health services to those at greatest risk, prevention is probably more important than treatment. Oral administration of high dose supplements (2000,000 IU every 3 to 6 months), vitamin A fortification of commonly consumed items, or best of all, increased dietary intake of natural sources of vitamin A will reduce the number of needlessly blind young children. Given recent evidence that vitamin A deficiency greatly increased overall mortality, even among children without evidence of xerophthalmia, the same prophylactic regimen may improve child survival by 35% or more. (6 figures, 1 table, 19 references)—Author's abstract

Journal Français D'Ophtalmologie

Long term functional results. Demailly, Ph., Gruber, D., and Kretz, G. (Service d'Ophtalmologie, Hôpital Saint-Joseph, 7 rue Pierre-Larousse, 75674 Paris Cedex 14, France). J. Fr. Ophtalmol. 12:527, 1989.

The functional results of the treatment of primary open angle glaucoma were analysed. A retrospective study was undertaken on 437 eyes from 282 patients (127 women, 145 men) followed in Saint Joseph's Hospital (Paris). The mean follow-up was 9.7 years (4–22 years). 265 eyes received only medical treatment, 83 eyes argon laser trabeculoplasty and 89 eyes surgery (66 trabeculectomies—23 cataract-glaucoma combined operations). At least twice a year, intraocular pressure, visual acuity and mean total visual capability on the Friedmann analyser were recorded on a computer. The severity gradient was calculated from the evolution gradient of total visual capability versus intraocular pressure with time for each group (medical, argon laser trabeculoplasty, surgery) before and after treatment. Medical severity gradient was not significantly different from argon laser trabeculoplasty severity gradient or surgery severity gradient (trabeculectomy or combined surgery). For each group, severity gradient before treatment was not significantly different from severity gradient after treatment. For tonometric failures after argon laser trabeculoplasty or surgery, severity gradient before treatment was not different from severity gradient after treatment. Nevertheless, after trabec-

ulectomy, in the cases of clear tonometric success (intraocular pressure ≤ 16 mm Hg), severity gradient was significantly improved (P ≤ .001). On the other hand, no positive influence was noted on visual field evolution in cases of a commonly admitted good tonometric control (intraocular pressure ≤ 21 mm Hg). Visual acuity loss after trabeculectomy was greatest during the first year (6/20). The cataractogenic role of trabeculectomy was statistically confirmed. The incidence of cataract at 5 years was 46%. This cataractogenic effect occurred significantly more after 55 years. The authors discussed tonometric effect on the total visual capability evolution. It seems necessary to have a good and constant tonometric success for visual field preservation but functional results depend also on visual acuity. (13 figures, 30 references)—Authors' abstract

Journal of Neurology, Neurosurgery, and Psychiatry

Abnormalities of horizontal gaze. Clinical, oculographic and magnetic resonance imaging findings. I. Abducens palsy. Bronstein, A. M., Morris, J., Du Boulay, G., Gresty, M. A., and Rudge, P. (Neuro-otology Unit, Inst. Neurol., Natl. Hospital, Queen Sq., London WC1N 3GB, United Kingdom.) J. Neurol. Neurosurg. Psychiatry 53:194, 1990.

Fifty-one patients with abnormalities of horizontal gaze were studied with magnetic imaging of the brain and eye movement recordings to identify the loci of lesions responsible for isolated abducens palsy, conjugate gaze palsy and different types of internuclear ophthalmoplegias. The lesions responsible for a particular disorder were identified by overlapping enlarged drawings of the individual scans at comparable brainstem levels and identifying the areas where the abnormal magnetic resonance imaging of the signals intersected. A statistical procedure was devised to exclude the possibility that the areas of overlap occurred by chance. In this paper, the findings in the group of patients with VI nerve palsy are reported since the location of their lesions could be predicted from known anatomy, so validating the procedure. The results were independently obtained with the overlapping technique and the statistical procedure and showed that the lesions were located in a region corresponding to the posterior part of the abducens fasciculus. This con-

firms that central lesions producing isolated lateral rectus weakness spare the abducens nuclei. The agreement between the procedures used and earlier clinical and experimental results suggest that the method the authors describe can be applied to locate the site of lesions on magnetic resonance imaging in other groups of patients with more complex gaze disorders. (3 figures, 2 tables, 25 references)—Authors' abstract

Abnormalities of horizontal gaze. Clinical, oculographic and magnetic resonance imaging findings. II. Gaze palsy and internuclear ophthalmoplegia. Bronstein, A. M., Rudge, P., Gresty, M. A., Du Boulay, G., and Morris. J. (Neuro-otology Unit, Inst. Neurol, Natl. Hospital, Queen Sq., London WC1N 3GB, United Kingdom). J. Neurol. Neurosurg. Psychiatry 53:200, 1990.

The site of lesions responsible for horizontal gaze palsy and various types of internuclear ophthalmoplegia was established by identifying the common areas where the abnormal magnetic resonance imaging signs from patients with a given ocular-motor disorder overlapped. Patients with unilateral gaze palsy had lesions in the paramedian area of the pons, including the abducens nucleus, the lateral part of the nucleus reticularis pontis caudalis and the nucleus reticularis pontis oralis. Patients with abducens nucleus lesions showed additional clinical signs of lateral rectus weakness. Lesions responsible for bilateral gaze palsy involved the pontine tegmental raphe. Since this region contains the saccadic omnipause neurons, this finding suggest that damage to omnipause cells produces slowing of saccades rather than opsoclonus, as previously proposed. All internuclear ophthalmoplegias, regardless of the presence of impaired abduction or convergence, had similar magnetic resonances imaging appearances. Frequently the lesions in patients with internuclear ophthalmoplegia, were not confined to the medial longitudinal fasciculus but also involved neighbouring structures at the pontine and mid-brain levels. There was a statistically significant association between the clinical severity of the internuclear ophthalmoplegia and the presence of abnormal abduction or convergence. The findings suggest that the lesions outside the medial longitudinal fasciculus, which may affect abducens, gaze or convergence pathways, are responsible for the presence of features additional to internuclear

ophthalmoplegia, depending on the magnitude of functional disruption they produce. (8 figures, 4 tables, 31 references)—Authors' abstract

Klinische Monatsblätter für Augenheilkunde

Biometric measurements of the anterior chamber before and after Nd:YAG laser iridectomy. Schrems, W., Hofmann, G., and Krieglstein, G. K. (Richard-Wagner-Str. 20, 8580 Bayreuth). Klin. Monatsbl. Augenheilkd. 196:128, 1990

In a prospective clinical study covering 41 eyes (28 patients) with narrow-angle glaucoma the central and peripheral anterior chamber depths were determined biomicroscopically before and after Nd:YAG laser iridectomy. In 29 eyes the central anterior chamber depth was also measured by ultrasonography. In contrast to the increase in central anterior chamber depth, which was only slight, the increase in the peripheral anterior chamber depth was statistically significant (P < .01). (4 figures, 1 table, 13 references)—Authors' abstract

Peripheral retinal neovascularization in diabetic retinopathy: fluorescein-angiographic classification and response to panretinal photocoagulation. Theodossiadis, G., and Micha, M. (Univ. Augenklinik Athen, 54 Omirou Str., GR-16072, Athens, Greece). Klin. Monatsbl. Augenheilkd. 196:143, 1990.

The prospective study reported here was based on 105 diabetic eyes with "new vessels elsewhere" (NVE) treated exclusively by panretinal laser application and followed up for 2.5 to 4 years. Fundus angiography was performed before treatment. The eyes were then classified in four categories according to the extent and location of capillary nonperfusion responsible for the "new vessels elsewhere" namely 1) generalized ischemia (Type A); 2) extensive midperipheral ischemia (Type B); 3) moderate midperipheral ischemia (Type C); and 4) peripheral ischemia (Type D). Analysis of the neovascularization distribution pattern showed that "new vessels elsewhere" alone existed only in peripheral ischemia, whereas in the other three types the neovascularization was present either only in the retina or in both the

retina and the optic disk. This mixed vascularization was 100% in generalized ischemia, 71% in extensive midperipheral ischemia, 31% in moderate midperipheral ischemia and nonexistent in peripheral ischemia. Statistical analysis revealed a significant correlation between the type of ischemia and the location of the new vessels. The therapeutic results 3-4 months, 1 year, and 2.5-4 years after intervention showed a significant trend toward an increase in the number of eyes with recurrences when moving from peripheral ischemia to generalized ischemia. This means that the prognosis of "new vessels elsewhere" after panretinal laser coagulation depends mainly on the type of retinal ischemia. The poorest prognosis is that for generalized ischemia (Type A), followed in descending order by extensive midperipheral ischemia (Type B), moderate midperipheral ischemia (Type C), and peripheral ischemia (Type D). The critical period for increased recurrence in cases which initially responded positively to treatment is primarily in the first 3-4 months following the intervention. (4 figures, 5 tables, 15 references)—Authors' abstract

Mayo Clinic Proceedings

Pulmonary complications from ophthalmic preparations. Prakash, U. B. S., and Rosenow, E. C. (Div. Thoracic Dis., Mayo Clin., Rochester, MN 55905). Mayo Clin. Proc. 65:521, 1990.

Topical β-adrenergic blocking agents are commonly used to treat glaucoma. Exacerbations of asthma and bronchospasm caused by topical β-adrenergic ophthalmic preparations are well known. The authors describe a 67-year-old woman who had aspiration pneumonitis characterized by a nodular infiltrate in the right middle lobe of the lung and nocturnal coughing after beginning topical application of an ointment (Lacri-Lube) for treatment of xerophthalmia. Bronchial washing demonstrated lipid-laden pulmonary alveolar macrophages. After the use of Lacri-Lube was discontinued, her cough and chest roentgenographic abnormality totally disappeared. The authors postulate that the topical ophthalmic preparation, which contains mineral oil and petrolatum, drained into the nasopharynx, trachea, and bronchial tree through the nasolacrimal duct and caused lipoid pneumonitis from aspiration of the oil contents. To the authors knowledge, this is the first report of pulmonary complica-

tions caused by Lacri-Lube. The authors briefly review the pulmonary complications, including pulmonary edema, apnea from paralysis of respiratory muscles, bronchospasm from non-β-adrenergic blocking drugs, and electrolyte abnormalities, attributable to topically and systemically administered ophthalmic medications. (2 figures, 1 table, 69 references)—Authors' abstract

Neurology

The characteristics and mechanisms of visual disturbances associated with anticonvulsant therapy. Remler, B. F., Leigh, R. J., Osorio, I., and Tomsak, R. L. (Dept. Neurol., Univ. Hospitals of Cleveland, 2074 Abington Rd., Cleveland, OH 44106). Neurology 40:791, 1990.

Eight epileptic patients receiving anticonvulsants had recurrent visual disturbances in the form of diplopia and oscillopsia in the horizontal or vertical planes. The symptoms could be ascribed to impaired vergence mechanisms, vertical nystagmus, or abnormalities of the vestibulo-ocular reflex. Other eye movements, such as pursuit and gaze-holding, were also affected, but did not lead to complaints. Episodes of visual disturbance were often preceded by prodromes of ocular or systemic discomfort, after which oscillopsia or diplopia evolve rapidly. The symptomatology was stereotyped but unique for each patient and may reflect idiosyncratic susceptibility to the ocular motor side effects of anticonvulsants. Six of the 8 patients were taking carbamazepine and phenytoin in combination, which have similar effects on the ocular motor system. (2 figures, 3 tables, 42 references)—Authors' abstract

Pupillary responses to dilute pilocarpine in preganglionic 3rd nerve disorders. Jacobson, D. M. (Neuro-ophthalmol. [4F], Marshfield Clin., 1000 N. Oak Ave., Marshfield, WI 54449). Neurology 40:804, 1990.

Supersensitivity of the iris sphincter to dilute parasympathomimetic agents is considered a diagnostic hallmark of a postganglionic oculomotor nerve disorder. Nine of 13 patients with preganglionic 3rd nerve palsies showed supersensitive pupillary responses using pilocarpine 0.1%. The presence of supersensitivity was not related to the cause of 3rd nerve dysfunction or interval time from onset to testing, but was

related to the extent of associated iris sphincter paresis. Some patients with long-standing preganglionic 3rd nerve palsies had features of postganglionic damage, including light-near dissociation and segmental paresis of the iris sphincter. These observations suggest that I mechanism of cholinergic supersensitivity in some chronic cases of preganglionic 3rd nerve disorders may be transsynaptic degeneration of postganglionic fibers. In another set of experiments, pharmacologically dilated pupils in normal subjects constricted more to dilute pilocarpine than their normal sized fellow pupils. Cholinergic supersensitivity in pupil-involving 3rd nerve palsies might also occur simply because the affected pupil is larger than the unaffected pupil. (1 figure, 1 table, 25 references)—Author's abstract

Ophthalmologia

Senile retinoschisis. Morphological relationship of the intraretinal spaces of retinal periphery with senile retinoschisis and schisis-detachment. Göttinger, W. (Innsbruck, Austria). Ophthalmologia 1:312, 1989.

Intraretinal spaces, the so-called peripheral cystoid degeneration, form the basis from which retinoschisis develop. In peripheral cystoid degeneration, the columns between the cysts become ruptured during the formation of retinoschisis. This division generally occurs at the level of the inner nuclear layer. The retinal columns described in peripheral cystoid degeneration probably consists of stretched cell processes (dendrites and neurites) and Müller cells. In peripheral cystoid degeneration, Müller's cells seem to play a role in the formation of basal membrane and collagenous microfibrils. These microfibrils aggregate into thick bundles and can wrap themselves around the retinal columns in a netlike fashion. After having been torn apart, the retinal columns together with their bases, fibrilar bundles, and basement membrane material form a "glious-fibrous" layer on the inner side of the outer layer of the schisis. The shrinking of this "glious-fibrous" layer is an important factor in the pathogenesis of outer layer holes. These outer layer holes lead to detachment of the outer layer of the schisis and of the surrounding healthy retina. It is questionable whether inner layer holes play any role at all in the formation of schisis detach-

ment. (14 figures, 65 references)—Author's abstract

Retina

Miosis during vitreoretinal surgery. Smiddy, W. E., Glaser, B. M., Michels, R. G., and Vitale, S. (Retina Ctr., Campus of St. Joseph Hosp., 7620 York Rd., Towson, MD 21204). Retina 10:42, 1990.

Maintenance of wide pupillary dilation during vitreoretinal surgery can be important in successful completion of the operation. This study identified factors associated with intraoperative miosis. Also, flurbiprofen, a topically applied nonsteroidal anti-inflammatory agent, was evaluated for its efficacy in preventing intraoperative miosis in a prospective, randomized study of 99 consecutive patients. Factors associated with intraoperative miosis included duration of surgery greater than 90 minutes, preoperative afferent pupillary defect, and recent previous surgery. Preoperative treatment with flurbiprofen did not decrease the risk of intraoperative miosis. (6 tables, 16 references)—Authors' abstract

NEWS ITEMS

Puerto Rico Medical Association: 22nd Annual Ophthalmology Convention

The Puerto Rico Medical Association: 22nd Annual Ophthalmology Convention will be held Oct. 11–14, 1990, at the Caribe Hilton Hotel in San Juan, Puerto Rico. For further information, write Victor M. Diaz Bonnet, M.D., Box 1184 Hato Rey, PR 00919; telephone (809) 765-9470.

American Society of Ophthalmic Plastic and Reconstructive Surgery: 21st Annual Scientific Symposium

The American Society of Ophthalmic Plastic and Reconstructive Surgery: 21st Annual Scientific Symposium will be held Oct. 27, 1990, in Atlanta, Georgia. For further information, write Paul T. Gavaris, M.D., Program Chairman, 1990, 4910 Massachusetts Ave. N.W., Washington, DC 20016; telephone (202) 686-1853.

Cullen Eye Institute, Baylor College of Medicine: 32nd Annual Course in Contact Lens Technology

The Cullen Eye Institute, Baylor College of Medicine: 32nd Annual Course in Contact Lens Technology will be held Nov. 29 to Dec. 1, 1990, in Houston, Texas. For further information, write Bette Burkett, Contact Lens Technology Course, Cullen Eye Institute, Baylor College of Medicine, Houston, TX 70030; telephone (713) 798-5942.

Johns Hopkins Medical Institutions: Diabetic Retinopathy in 1990

The Johns Hopkins Medical Institutions: Diabetic Retinopathy in 1990 will be held Nov. 16, 1990, in Baltimore, Maryland. For further information, write Program Coordinator, The Johns Hopkins Medical Institutions, Office of Continuing Education, Turner Building, 720 Rutland Ave., Baltimore, MD 21205; telephone (301) 955-2959.

Manhattan Eye, Ear & Throat Hospital—The Diabetic Eye: Disease and Treatment

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold a course entitled The Diabetic Eye: Disease and Treatment on Sept. 15, 1990, in New York City. For further information, write Kimberly Corbin, Course Coordinator, Department of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761.

Medical College of Wisconsin: Ocular and Orbital Tumor Symposium

The Medical College of Wisconsin: Ocular and Orbital Tumor Symposium will be held Dec. 7 and 8, 1990, at the Wyndham Milwaukee Center in Milwaukee, Wisconsin. For further information, write William F. Mieler, M.D., 8700 W. Wisconsin Ave., Milwaukee, WI 53226; telephone (414) 257-5544.

New York University Medical Center: Basic Science Course in Ophthalmology

The New York University Medical Center: Basic Science Course in Ophthalmology will be held Sept. 5, 1990, and Dec. 21, 1990, in New York City, New York. For further information, write NYU Medical Center, Post-Graduate Medical School, 550 First Ave., New York, NY 10016; telephone (212) 340-5295.

West Virginia University Department of Ophthalmology: 11th Annual Clinical Conference

The West Virginia University Department of Ophthalmology: 11th Annual Clinical Conference will be held Oct. 19 and 20, 1990, in

Morgantown, West Virginia. For further information, write Patricia Schumann, Conference Coordinator, Department of Ophthalmology, WVU Health Sciences Center North, Morgantown, WV 26506; telephone (304) 293-2757.

American Society of Ophthalmic Registered Nurses: Annual Meeting

The American Society of Ophthalmic Registered Nurses: Annual Meeting will be held Oct. 28–31, 1990, in Atlanta, Georgia. For further information, write Audie Ahn Haggard, ASORN, Inc. Headquarters, P.O. Box 3030, San Francisco, CA 94119; telephone (415) 561-8513.

Manhattan Eye, Ear & Throat Hospital: Future Focus—A Career Planning and Practice Management Program

Allergan Pharmaceuticals and the Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold a course entitled Future Focus: A Career Planning and Practice Management Program for Ophthalmology Residents, Fellows, Recent Graduates, and their Spouses on Sept. 8, 1990, in New York City. For further information, write Kimberly Corbin, Course Coordinator, Department of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; Fax (212) 753-7699.

American Ophthalmological Society: 1990–1991 Officers

Frederick C. Blodi of Iowa City was elected president of the American Ophthalmological Society to succeed Robert E. Kennedy of Rochester, New York, at the May 1990 meeting. Thomas P. Kearns of Rochester, Minnesota, was elected vice president to succeed Dr. Blodi. W. Banks Anderson of Durham, North Carolina, was re-elected secretary-treasurer; Robert B. Welch of Baltimore was re-elected editor of the Transactions; and William Tasman of Philadel-

phia was named assistant editor. W. Richard Green of Baltimore was named to the Council.

St. Louis Ophthalmological Society: 1990–1991 Officers

The following officers for 1990–1991 were elected at the annual meeting of the St. Louis Ophthalmological Society: Stephen R. Waltman, president; Robert D. Lewis, vice president; and Allen F. Tess, secretary-treasurer.

_____ Personals _____

Richard F. Brubaker

The Von Sallmann Prize in Vision and Ophthalmology for 1990 was awarded to Richard F. Brubaker, Professor of Ophthalmology at the Mayo Medical School in Rochester, Minnesota. The prize was awarded at the 9th International Congress of Eye Research in Helsinki, Finland, July 29 to Aug. 4, 1990.

Richard Keates

The official announcement of the establishment of the Irving Leopold Chair in Ophthalmology and the appointment of Richard Keates to the chair was made May 8, 1990, at the University of California, Irvine. Dr. Keates met and served under Dr. Leopold at the Wills Eye Hospital when Leopold was Chief of Ophthalmology.

Howard Schatz

Howard Schatz gave the 2nd Annual Vallottan Lecture at the Medical University of South Carolina's Ophthalmology Update Course, in Charleston, in May 1990.

Elias I. Traboulsi

Elias I. Traboulsi has been named assistant professor at the Johns Hopkins Center for Hereditary Eye Diseases of the Wilmer Eye Institute.

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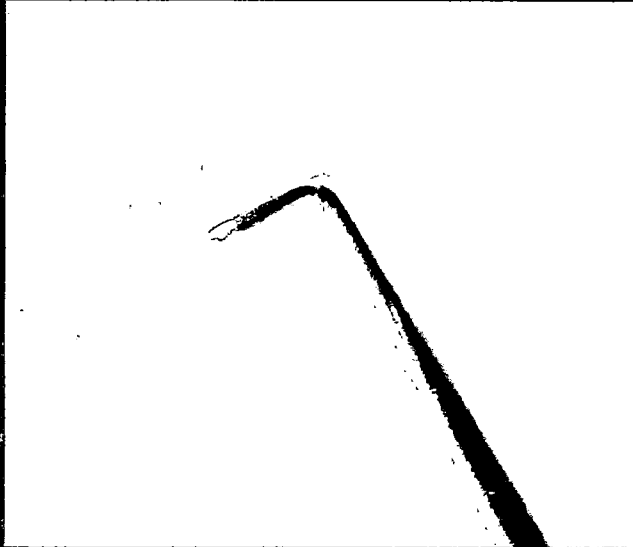
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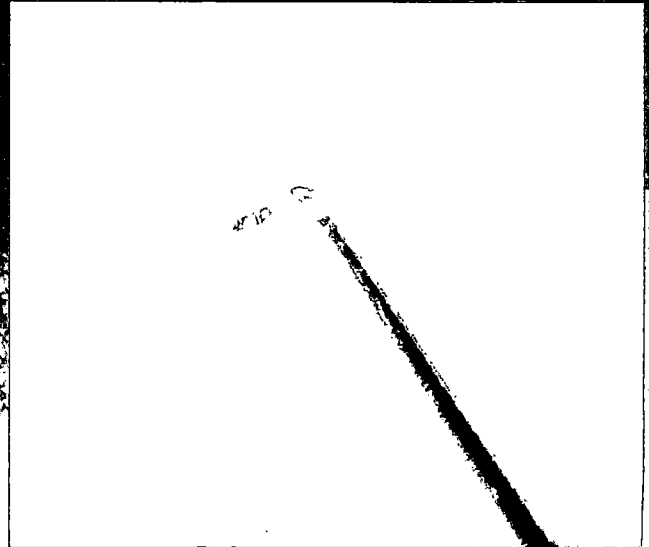
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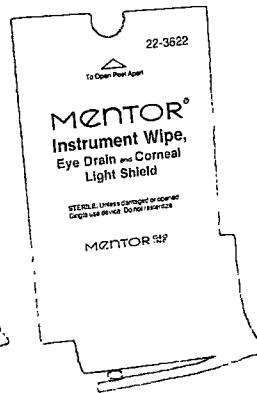
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Visual Prognosis in Macular Retinoblastomas

Byron L. Lam, M.D., G. Frank Judisch, M.D., Warren M. Sobol, M.D.,
and Christopher F. Blodi, M.D.

Since 1979, we have treated 11 patients who had macular retinoblastomas. Two patients eventually recovered 20/20 visual acuity despite the presence of subretinal fluid in the fovea at the time of diagnosis. The diagnosis was made at 11 and 14 months of age, and follow-up periods were ten and seven years, respectively. One case was sporadic and the other was hereditary. Both patients were treated with external radiation; one patient was also treated with chemotherapy. The lesions regressed markedly after treatment. These cases demonstrate that visual prognosis in macular retinoblastomas is not uniformly poor even when a foveal detachment is present. Visual acuity may be good in some cases, which supports the merits of medical treatment rather than enucleation in selected patients.

THE VISUAL PROGNOSIS of macular retinoblastoma is usually poor. Although macular involvement alone is not necessarily an indication for enucleation in either unilateral or bilateral cases, enucleation is the preferred treatment in eyes where visual prognosis is poor.[1] Until recently, enucleation was the accepted treatment for sporadic, unifocal retinoblastomas, irrespective of the tumor stage. We treated two patients who had macular retinoblastomas and foveal detachments, and both patients retained their eyes and 20/20 visual acuity. We also reviewed all cases of macular retinoblastoma treated at our institution from 1979 to 1988 to help to place these two cases in perspective.

Case Reports

Case 1

In May 1979, we examined a healthy 11-month-old girl who had 15 prism diopters of left esotropia of four months' duration. There was no family history of retinoblastoma, and the results of parental ophthalmoscopic examinations were normal. The patient's fixation was central, steady, and maintained in the right eye but central, steady, and unmaintained in the left eye. Results of examination under anesthesia disclosed two retinoblastomas in the right eye, a macular lesion with subfoveal retinal fluid, and a small superior peripheral lesion (Fig. 1). Clinically, the edge of the macular lesion was approximately 1 disk diameter from the fovea. The left eye, which had multiple retinoblastomas with a total retinal detachment, was enucleated. Cryotherapy was applied to the peripheral lesion in the right eye, and the posterior lesion was treated with external radiation (45 Gy in 25 fractions). Results of systemic examination by the pediatric oncology service were unremarkable. The patient also received intravenous chemotherapy (vincristine sulfate, 1.0 mg/m², and cyclophosphamide, 300.0 mg/m² weekly) for 52 weeks as recommended by the St. Jude Children's Research Hospital (Memphis, Tennessee) protocol in effect at that time.

Results of serial fundus examinations showed regression of the macular lesion (Fig. 1). In
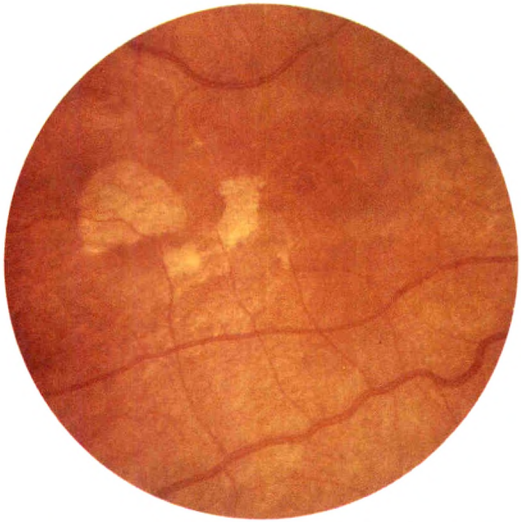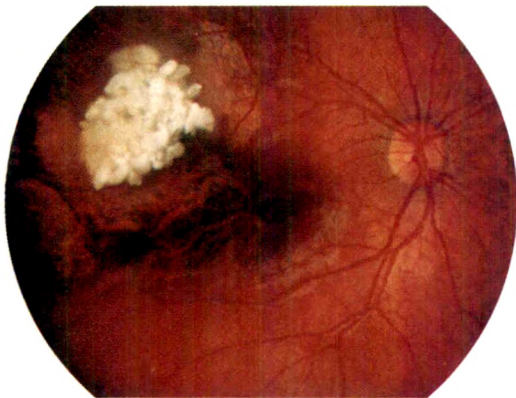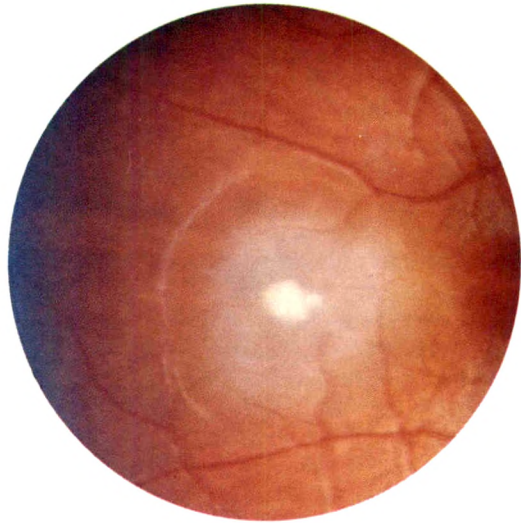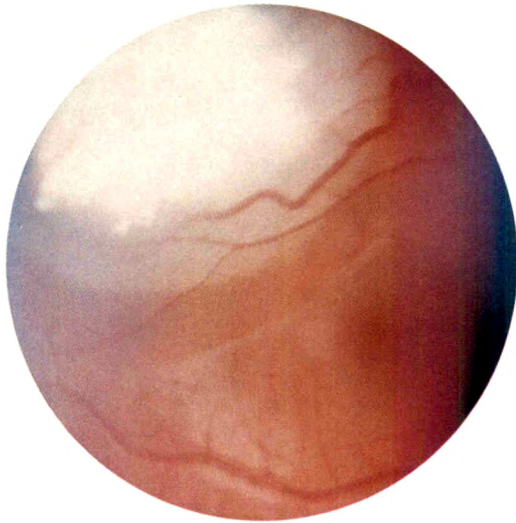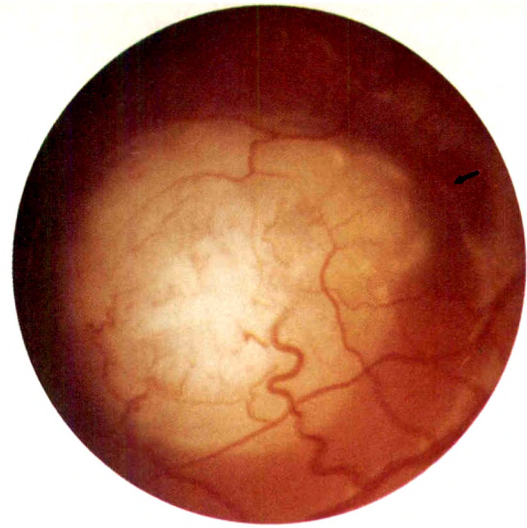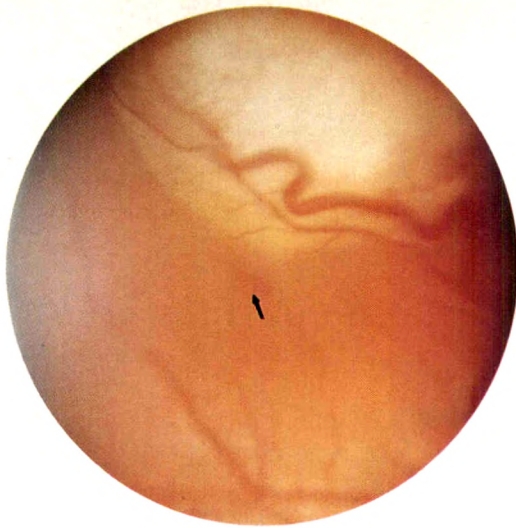
Fig. 1 (Lam and associates). Right fundus of Case 1. Top, Fundus at the time of initial examination in March 1979 showing a macular retinoblastoma with subretinal fluid at the fovea (arrow). Middle, Three months later the lesion had regressed markedly after radiation treatment. Bottom, Six years later the fundus showed regressed retinoblastoma lesion.

Fig. 2 (Lam and associates). Right fundus of Case 2. Top, Fundus at the time of initial examination in April 1983 demonstrating a macular retinoblastoma with subretinal fluid at the fovea (arrow). Middle, Six months later the lesion had regressed markedly after radiation treatment. Bottom, Four years later the fundus showed regressed retinoblastoma lesion.

November 1982, visual acuity was 20/30 with line pictures, and by June 1985, the visual acuity was 20/20 with line letters. When the patient was last examined in August 1989, the uncorrected visual acuity was 20/20, the lens was clear, and no radiation retinopathy was evident. Mild midfacial hypoplasia attributable to previous radiation treatment was apparent.

Case 2

In April 1983, a 14-month-old girl was examined because an older brother had unifocal retinoblastoma. Although the results of an ocular examination of the parents were normal, there was a family history of unilateral retinoblastoma and unilateral retinoblastoma with pinealoma in paternal cousins. The patient's fixation was central, steady, and unmaintained in the right eye and central, steady, and maintained in the left eye. No strabismus or other externally visible abnormalities were noted. Examination under anesthesia showed a macular retinoblastoma approximately 1 disk diameter from the fovea in the right eye (Fig. 2). The fovea was detached with subretinal fluid. The results of a systemic examination by the pediatric oncology service were unremarkable. The right eye was treated with external radiation (45 Gy in 25 fractions). Regression of the retinoblastoma was rapid and complete (Fig. 2). In June 1988, visual acuity was 20/20 with line letters in both eyes. On the Titmus stereoscopic test, the patient had 40 arc-seconds of stereoacuity. When the patient was last examined in June 1990, the uncorrected visual acuity was 20/20 in both eyes. There was no strabismus and no radiation retinopathy. She continued to maintain 40 arc-seconds of stereoacuity.

Patients and Methods

After obtaining a list of patients with retinoblastoma from the tumor registry at the University of Iowa Hospitals and Clinics, we reviewed the records and photographs of these patients.

Results

From 1979 to 1988, retinoblastoma was diagnosed in 39 patients at our institution. Of the 39 patients, 25 (64%) had sporadic, unifocal retinoblastomas; seven (18%) had bilateral retinoblastomas with notable family histories; six (15%) had sporadic, bilateral retinoblastomas; and one (3%) (Case 2) had a unifocal retinoblastoma with a notable family history. Of the total 52 eyes, 36 (69%) were enucleated. Of these 36 eyes, 33 had multiple tumors with some lesions greater than 10 disk diameters (Reese-Ellsworth group IV-A), a tumor anterior to the ora serrata (Reese-Ellsworth group IV-B), massive tumors involving over half of the retina (Reese-Ellsworth group IV-A), or vitreous seeding of the tumor (Reese-Ellsworth group IV-B).[2] The three remaining eyes had solitary tumors behind the equator of greater than 10 disk diameters (Reese-Ellsworth group III-B).[2]

Of the 16 eyes we treated, 11 had macular retinoblastomas. One patient had recurrence of the tumor after treatment, and the eye was enucleated. Another patient also had congenital cataracts and microphthalmos. The treatment results of the remaining nine patients are summarized in the Table. The macula was divided into four quadrants vertically and horizontally through the fovea, and the number of quadrants with retinoblastoma was recorded. The extent of foveal involvement (foveal diameter = 500 mm) was also noted. Aside from the two patients presented in the case reports, the other seven patients all had bilateral retinoblastomas and were treated with external radiation. All patients were followed up with indirect ophthalmoscopy and indentation under general anesthesia.

Discussion

Retinoblastoma has traditionally been treated with enucleation of the affected eye.[1] This is especially true in unilateral cases where the visual prognosis is judged to be poor. In bilateral cases, the more affected eye is enucleated and the better eye is treated with a variety of modalities such as cryotherapy, photocoagulation, chemotherapy, external beam radiation, and episcleral plaque radiation, depending on the tumor location and response to therapy.[3] Recently, nonenucleation treatment in both unilateral and bilateral cases of retinoblastoma has been proposed for unifocal and multiple tumors of less than 10 disk diameters without ora serrata extension or vitreous seeding (Reese-Ellsworth group I through III).[2, 4-6]

The visual prognosis of macular retinoblastoma is usually poor. Holbek and Ehlers[7] de-

TABLE

NINE PATIENTS WITH MACULAR RETINOBLASTOMAS

CASE NO., AGE	NO. OF QUADRANTS INVOLVED	FOVEAL INVOLVEMENT	FOLLOW-UP PERIOD (YRS)	CURRENT VISUAL ACUITY
1, 11 mos	2	Detached	10.0	20/20
2, 14 mos	2	Detached	7.0	20/20
3, 1 mo	1	None	10.0	20/20
4, 5 mos	2	Tumor	10.0	Hand motions
5, 1 mo	1	None	2.5	Central, steady, and maintained
6, 1 wk	2	None	2.0	Central, steady, and maintained
7, 3 mos	4	Tumor	3.0	Central, steady, and maintained
8, 2 wks	4	Tumor	2.5	Central, steady, and unmaintained
9, 2 mos	4	Tumor	2.0	Not central, unsteady, and unmaintained

scribed seven patients with macular retinoblastomas treated with radiation in which the final visual acuity ranged from 20/100 to counting fingers with follow-up periods of 12 to 17 years. In our series, three of the nine patients eventually attained 20/20 visual acuity (Table). These three patients had no direct foveal involvement by the tumor, but two of the patients had foveal detachments. Of the remaining six patients, one patient retained hand motions visual acuity, and five patients were still too young to obtain a line letter visual acuity.

Our two cases had a retinoblastoma close to the fovea with foveal detachments. With radiation therapy in both patients and chemotherapy in one, the lesions regressed. Both patients maintained 20/20 visual acuity in the affected eye ten and seven years later, respectively. The presence of 40 arc-seconds of stereoacuity in the second patient indicated bifoveal fixation. Hence, foveal detachment alone does not necessarily indicate a poor visual prognosis.

These cases support the concept of initial nonenucleation treatment of selected patients with posterior pole retinoblastomas. Not only will eyes be preserved, but normal central vision and bifoveal fixation may be attained in some cases.

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Evaluation of Acute Radiation Optic Neuropathy by B-scan Ultrasonography

Alfred A. Lovato, M.D., Devron H. Char, M.D., Jeanne M. Quivey, M.D., and Joseph R. Castro, M.D.

We studied the accuracy of B-scan ultrasonography to diagnose radiation-induced optic neuropathy in 15 patients with uveal melanoma. Optic neuropathy was diagnosed by an observer masked as to clinical and photographic data. We analyzed planimetry area measurements of the retrobulbar nerve before and after irradiation. The retrobulbar area of the optic nerve shadow on B-scan was quantitated with a sonic digitizer. Increased optic nerve shadow area was confirmed in 13 of 15 patients who had radiation optic neuropathy (P < .004). The correct diagnosis was confirmed when the results of ultrasound were compared to fundus photography and fluorescein angiography. In 13 patients there was acute radiation optic neuropathy. Two patients did not show an enlarged retrobulbar optic nerve, and the clinical appearance suggested early progression to optic atrophy. Ultrasonography documents the enlargement of the optic nerve caused by acute radiation changes.

RADIATION THERAPY has been used in the management of ocular tumors since 1929; however, a number of issues remain unresolved.[1,2] We have treated more than 600 patients with either helium ion charged particles or iodine 125 brachytherapy. Treatment failed in less than 5% of the patients, and more than 90% of the eyes have been retained.[3,4] Ocular irradiation has a number of complications.[1-4] Char and associates[3,4] have reported that approximately 10% of the patients have developed radiation-induced optic neuropathy. The tumors were almost always those located within 3 mm of the optic nerve. The distance from the posterior edge of the tumor to the optic nerve averaged approximately 2 mm, and the average latency to diagnosis of optic neuropathy was 12 months.

Diagnosis of radiation optic neuropathy can sometimes be difficult. We examined in a masked manner the accuracy of B-scan ultrasonography in the establishment of this diagnosis.

Patients and Methods

All patients were examined in the Ocular Oncology Unit at the University of California, San Francisco, between 1981 and 1988. Complete ocular examinations were performed, and the diagnosis of a uveal melanoma was made on the basis of a number of studies using noninvasive techniques. No patient had evidence of optic neuropathy before therapy.

The criteria for the patients studied were as follows: melanoma of the choroid; evidence of optic neuropathy after irradiation based on ophthalmoscopy, fundus photography, or fluorescein angiography; B-scan ultrasonography obtained within one week of the development of optic neuropathy; and two years or more of observation after irradiation.

The localization procedure and details of treatments have been previously described.[3,4] Patients received between 50 and 80 gray equivalents (GyE) of helium ion external beam or iodine 125 brachytherapy. Helium ion therapy was performed in five outpatient fractions

over an eight- to 11-day period. Iodine 125 brachytherapy was performed by suturing a radioactive plaque onto the sclera in an area adjacent to the choroidal melanoma, usually for a period of approximately four days, to achieve a dose of 70 or 80 Gy to the tumor apex.

All patients were examined at six weeks and every three to four months with standard clinical tests, ultrasonography, fundus photography, and fluorescein angiography.

Ophthalmoscopic signs of acute radiation optic neuropathy included disk swelling, peripapillary hard exudates, hemorrhages, and cotton-wool spots (Fig. 1). This progressed usually to early optic atrophy within three months. The vascular changes regressed, and the nerve fiber layer and the nerve began to whiten.

We analyzed the ultrasound patterns of 15 patients who developed clinical findings consistent with the diagnosis of radiation optic neuropathy. The posttreatment retrobulbar optic nerve ultrasound pattern was compared to the pretreatment pattern in a masked fashion. Each ultrasound examination was performed by a single technician, and we used the conventional anteroposterior B-scan ultrasound image through the cornea, lens, and optic nerve. Each study was performed at the same gain settings. The ultrasound diagnosis of radiation optic neuropathy was based on serial enlargement of the optic nerve shadow.

Verification of optic nerve shadow enlargement by B-scan ultrasonography was accomplished by planimetry using a digitizer. This technique allowed quantification of the area subtended by the optic nerve pattern. The area

Fig. 2 (Lovato and associates). Left, Retrobulbar optic nerve shadow in an eye before irradiation. Right, Enlargement of retrobulbar optic nerve. The increased area is indicated by hatching.

of the retrobulbar optic nerve shadow between the retina and a distance 2 cm posterior to the retina was included in this measurement, as shown schematically in Figure 2. Statistical comparisons were performed with the Wilcoxon signed rank test.[5]

Results

Patient and ultrasound characteristics are listed in the Table. Ultrasonographic as well as fluorescein and photographic data were obtained within one week of the initial examination for apparent optic neuropathy. Results of fundus photography and fluorescein angiography confirmed the presence of optic neuropathy in 13 patients. In two cases where optic nerve enlargement by ultrasound could not be documented, fundus photography and fluorescein angiography also disclosed that the optic neuropathy had progressed to an atrophic stage. All patients had a history of a dramatic visual loss; two patients without enlargement of the optic nerve had noted diminished vision for approximately three months. The mean change in retrobulbar optic nerve area from pretreatment to the time of clinical diagnosis after irradiation was 0.199 cm^2 (range, 0.119 to 0.491 cm^2; standard deviation, ± 0.182 cm^2). The difference was statistically significant (P < .004) by using the Wilcoxon signed rank test.

Discussion

Stallard[1] first described radiation optic neuropathy in the fundi of patients with retinal capillary hemangiomas and retinoblastomas af-

Fig. 1 (Lovato and associates). Irradiated macular melanoma with optic neuropathy.

TABLE

ULTRASOUND DATA ON PATIENTS WITH RADIATION OPTIC NEUROPATHY

PATIENT NO.	RADIOTHERAPY*	LARGEST TUMOR DIAMETER (MM)	ULTRASOUND HEIGHT (MM)	DISTANCE TO NERVE (MM)	RETROBULBAR OPTIC NERVE AREA		TIME TO ONSET (MOS)	DOSE (GY)
					PRETREATMENT MEASURE (CM²)	POSTTREATMENT MEASURE (CM²)		
1	H	9.00	6.13	0.00	0.494	0.780	5.8	70
2	H	6.00	3.45	0.00	0.293	0.563	8.5	80
3	H	9.00	4.50	2.00	0.521	0.989	15.7	80
4	I	6.00	3.06	0.00	0.846	1.051	12.9	50
5	H	18.00	7.47	2.50	0.240	0.531	15.8	50
6	H	9.00	4.76	0.00	0.850	0.942	14.3	50
7	H	9.00	5.36	4.00	0.530	0.018	14.3	70
8	I	9.00	7.28	0.00	0.163	0.400	15.7	80
9	H	9.00	9.00	0.00	0.387	0.638	11.7	70
10	H	12.00	10.53	3.00	0.540	0.557	15.0	78
11	I	9.00	6.32	2.00	0.470	0.537	10.2	71
12	I	14.00	6.70	7.50	0.450	0.635	11.5	70
13	I	9.00	5.36	0.80	0.454	0.335	10.0	75
14	H	13.00	5.75	0.50	0.333	0.686	29.5	70
15	I	7.50	4.79	0.00	0.320	0.209	20.0	70

*H indicates helium ion therapy, and I indicates iodine 125 brachytherapy.

ter radon seed implantation in 1933. Radiation optic neuropathy involving the anterior optic nerve is characterized by hyperemic disk swelling, often accompanied by peripapillary hemorrhages, hard exudates, and subretinal fluid. Areas of capillary nonperfusion overlying the optic nerve head and within the retina are usually observed on fluorescein angiography.[6] Usually there was rapid evolution, within three months vascular changes were no longer apparent clinically, and early optic atrophy was noted.

The presumed mechanism of injury is radiation-induced vascular damage. Ross, Rosenberg, and Friedman[7] studied eyes that had been irradiated with 60 Gy of cobalt-60 plaque radiotherapy for orbital epidermoid carcinoma. The optic nerve in these patients disclosed large areas of necrosis with round cell infiltrate, occasionally polymorphonuclear infiltrate, and a reactive astrocytosis. Vessels within the optic nerve showed a variety of histopathologic changes, which included proliferation of the endothelial cells and thickening of the vessel walls with fibrinoid necrosis. Several vessels showed narrowed or obliterated lumens.[7] Similar data have been reported by Atkinson, Allen, and Gordon[8] and Sheline, Wara, and Smith.[9]

Latency periods from radiotherapy to the clinical detection of radiation-induced optic neuropathy appear to be about one year. These findings are similar to those of Brown and associates,[6] who noted radiation optic neuropathy in patients with uveal melanomas treated with cobalt-60 plaques. They noted optic nerve damage with 120 Gy of cobalt-60 brachytherapy as compared with 55 Gy of photon irradiation.[6]

Coleman and Carroll[10] described B-scan ultrasonographic changes in 24 patients with nonradiation-induced optic neuropathy. B-scan ultrasonography demonstrated optic nerve abnormalities in all but one patient with acute optic neuropathy. The changes identified varied from faint reduplication of the optic nerve outline to marked doubling of the nerve echo pattern with shadowing in the region of the fascia and enlargement of the extraocular muscle outline.[10]

In our patients, acute radiation optic neuropathy was identified correctly in 13 of 15 patients by using B-scan ultrasonography, and enlargement of the retrobulbar optic nerve shadow was the most common abnormality noted. The digital analyzer confirmed enlargement of the optic nerve shadow area in 13 of 15 patients. In the two exceptions, failure to document enlargement of the retrobulbar optic nerve was in agreement with results of fundus photography and fluorescein angiography. In these patients

the disease had probably evolved to the atrophic stage.

The incidence of radiation optic neuropathy will probably increase as these radiation modalities are used more frequently for posterior pole uveal melanomas, especially in cases in which the optic nerve cannot be shielded because of either tumor proximity or increased tumor thickness.

The diagnosis of acute radiation-induced optic neuropathy can usually be made by direct clinical examination. In atypical cases, additional diagnostic techniques such as ultrasonography can help confirm the diagnosis. Although these data are statistically significant, there are a number of caveats. In the immediate postoperative period transient enlargement of the optic nerve shadow could develop from surgical trauma or edema, although we have not observed this occurrence. We have not observed late optic nerve enlargement as a surgical irradiation sequela in the absence of acute optic neuropathy. Ten patients were studied who had peripapillary tumors, good vision, and no evidence of optic nerve enlargement (unpublished data); no ultrasonic evidence of optic nerve abnormalities were found. Rarely extraocular extension or tumor regrowth could mimic the ultrasound pattern we observed, although there is usually obvious intraocular tumor regrowth in such patients. Technical problems could also limit the utility of this technique. Correct probe orientation, standardized gain settings, and uniform planimetry criteria are necessary to ensure reproducible results.

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OPHTHALMIC MINIATURE

Barbara Berowne turned her remarkable violet-blue eyes on Dalgliesh and he was for a second disconcerted. After the first fleeting glimmer of curiosity the glance was deadened, almost lifeless, as if he were looking into coloured contact lenses. Perhaps after a lifetime of seeing the effect of her gaze she no longer needed to animate it with any expression other than a casual interest.

P. D. James, *A Taste For Death*
New York, Alfred A. Knopf, 1986, pp. 105-106

Histologic Study of Eyes With Transsclerally Sutured Posterior Chamber Intraocular Lenses

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We studied the postmortem histologic characteristics of two eyes that had undergone penetrating keratoplasty and transscleral suturing of a posterior chamber intraocular lens for bullous keratopathy. The eyes were studied three days postoperatively in a 79-year-old man with pseudophakia and six months postoperatively in an 83-year-old man with aphakia. We also removed a posterior chamber intraocular lens in a 73-year-old woman who had an epithelial downgrowth three months postoperatively. In the first two cases, only one of four haptics was successfully positioned in the sulcus. Histologic study disclosed a thin fibrous capsule surrounding the haptics at their attachment site, no inflammation around the transscleral portion of the suture, and exposure of a suture tip externally. In the third case, the intraocular lens fell back into the vitreous cavity after the fixation sutures were cut externally at the time of surgical removal. Stability of the lens in all three cases was primarily a result of intact transscleral sutures and not fibrous encapsulation or ciliary sulcus placement of haptics.

IN THE EVENT of a disrupted posterior capsule, transsclerally sutured posterior chamber intraocular lenses are an alternative to the placement of an anterior chamber intraocular lens or an iris sutured posterior chamber lens.[1-9] Histologic studies of posterior chamber intraocular lenses indicate that they are relatively well tolerated in the eye, particularly when compared to anterior chamber lenses.[10,11] However, posterior chamber lenses have been shown to activate complement in vitro.[12,13] Clinically, erosion of haptics into the ciliary body with associated inflammation, fibrosis, and glaucoma can occur.[14]

Postmortem and histologic examination of four eyes with iris sutured posterior chamber intraocular lenses has been reported.[15] Only one of eight haptics was placed successfully in the ciliary sulcus as intended. No fibrosis of haptics to the ciliary body was noted. Only one patient had a small focal infiltrate of chronic inflammatory cells in the ciliary body stroma adjacent to the lens haptic. Stability of the iris sutured posterior chamber lens was derived primarily from the optic attachment to the iris by sutures and to a lesser extent by haptic placement.

Transsclerally sutured lenses are stabilized by the fixation sutures and the presumed placement of haptics in the ciliary sulcus. Numerous techniques have been described to increase the chance of correct positioning, although no surgical technique guarantees sulcus placement of the haptic. There is limited clinical experience with transscleral suture removal. Johnson[7] observed no lens dislocation in five cases in which all transscleral sutures were removed three to four months postoperatively. Heilskov and associates[16] documented delayed lens dislocation after transscleral suture removal. The contribution in these cases from residual capsular flaps, haptic placement in the sulcus, or fibrosis into the ciliary body is unknown, since direct examination of haptic attachment was impossible. We studied the postmortem and histologic characteristics of two eyes with transsclerally sutured posterior chamber lenses and removed one such lens surgically.

Case Reports

Case 1

A 79-year-old man with pseudophakic bullous keratopathy in the left eye underwent a penetrating keratoplasty, anterior vitrectomy, removal of an anterior chamber lens, and placement of a transsclerally sutured posterior chamber intraocular lens on Jan. 25, 1989 with local anesthesia. Limbal conjunctival peritectomies and partial-thickness scleral flaps were prepared at the 8 o'clock and 2 o'clock meridians. A large Flieringa ring was attached.

A posterior chamber lens with a 7.0-mm polymethylmethacrylate optic and 14.0-mm angled blue polypropylene modified C-loops was used. A single-armed polypropylene suture on CIF-4 needles was tied 2.0 mm proximal to the haptic tips and set aside. An 8.0-mm donor cornea was prepared, and a 7.5-mm host button was removed. An anterior chamber lens removal and anterior vitrectomy were completed.

Transscleral sutures were passed behind the iris and through ciliary sulcus ab externo 1.0 mm posterior to the surgical corneoscleral limbus. Each lens haptic was inserted while pulling up on the fixation suture. The suture was passed through partial-thickness sclera, tied to itself, and cut short. The scleral flaps were placed over the suture ends closed with 10-0 nylon sutures under conjunctival flaps. The graft was sewn into place with 10-0 nylon sutures.

On the first postoperative day visual acuity was counting fingers. The fixation sutures were well covered. The graft was clear with mild striae and no epithelial defect. The anterior chamber had mild cell and flare, and the pupil was round. The lens was in good position. Topical prednisolone acetate 1% and gentamicin 0.3% were started. The patient died suddenly three days after the operation from a presumed pulmonary embolus. The right globe was obtained four hours post mortem for histologic examination.

Case 2

An 83-year-old man had undergone an intracapsular cataract extraction in the left eye in 1980. He developed aphakic bullous keratopathy and a dense corneal scar in the left eye. Visual acuity decreased to hand motions, which was consistent with direct ophthalmoscopic examination. In the right eye, visual acuity improved to 20/70 after extracapsular cataract extraction and intraocular lens implant in 1985. Visual acuity decreased gradually to counting fingers in the right eye over the next three years as a result of age-related macular degeneration.

The patient underwent a penetrating keratoplasty, anterior vitrectomy, and a transsclerally sutured posterior chamber lens in the left eye on Nov. 21, 1988. With local anesthesia, limbal conjunctival peritectomies were made at the 8 o'clock and 2 o'clock meridians. A large Flieringa ring was sutured onto the globe. A Bechert-style, polymethylmethacrylate posterior chamber intraocular lens with a 7.0-mm optic and 14.0-mm diameter was selected for transscleral fixation. Each haptic had a positioning hole at its distal end and a notch at the 12 o'clock and 6 o'clock meridians. A 10-0 polypropylene suture on a CIF-4 needle was preplaced between the positioning hole and notch of each haptic. An 8.5-mm donor cornea and an 8.0-mm host were trephined, and an anterior vitrectomy was performed.

Each suture was passed through the pupil and carefully advanced, tenting up the iris at 0.5-mm intervals as the needle tip approached the ciliary sulcus. When no movement of iris was noted, the needle was passed through the sclera and exited approximately 2.0 mm behind the surgical corneoscleral limbus. The lens was inserted, and each haptic was guided toward the ciliary sulcus as the transscleral suture was pulled up. The suture was passed through partial-thickness sclera, tied to itself, and cut short. The conjunctival flaps were pulled over the knots and sutured into place. The donor cornea was sutured with interrupted and running 10-0 nylon sutures.

Visual acuity was counting fingers on the first postoperative day. The polypropylene sutures were well covered. The graft was clear with moderate striae and no epithelial defects. The anterior chamber had moderate cell and flare. The iris remained unchanged with a large superior sector iridectomy. The intraocular lens was in good position. Prednisolone acetate 1% and tobramycin 0.3% were started. At four weeks postoperatively, visual acuity remained counting fingers. The fundus had diffuse macular pigmentary changes. The graft cleared and the anterior chamber quieted. The lens remained in position with the sutures covered by conjunctival flaps. Three months postoperatively, a large squamous cell carcinoma of the tongue with metastases to regional lymph nodes was dis-

covered. The patient died on May 10, 1989, six months after the operation. The left globe was obtained two hours post mortem for histologic examination.

Case 3

A 73-year-old woman underwent a penetrating keratoplasty, anterior chamber reconstruction with anterior chamber intraocular lens removal, anterior vitrectomy, and placement of a transsclerally sutured posterior chamber intraocular lens in the left eye on July 14, 1988. Three days postoperatively a leak around the host side of an interrupted 10-0 nylon suture at the 12 o'clock meridian was noted. The anterior chamber remained well formed. This leak was observed and sealed spontaneously. Three months postoperatively, the patient developed progressive glaucoma that became unresponsive to maximal medical therapy. The patient underwent two treatments with cyclocryotherapy and was referred to one of us (E.J.H.) for control of continued high intraocular pressures.

When examined nine months postoperatively, visual acuity was 20/200. Results of a slit-lamp examination disclosed moderate diffuse injection of the conjunctiva. Loops of 10-0 polypropylene were seen beneath conjunctival flaps, 2.0 mm posterior to the surgical corneoscleral limbus at the 3 o'clock and 9 o'clock

meridians. The graft was thin and clear with an endothelial line noted between the 11 o'clock and 3 o'clock meridians, which extended 1 mm onto the graft. The anterior chamber had mild cell and flare. Scattered peripheral anterior synechiae were noted. The intraocular lens was in good position. Intraocular pressure was 35 mm Hg. Argon laser applied to the iris surface confirmed the presence of a membrane. The clinical diagnosis of epithelial downgrowth was made.

In March 1988, the patient underwent an 8.5-mm penetrating keratoplasty and removal of a Youen's-style, polymethylmethacrylate posterior chamber intraocular lens with a 7.0-mm optic and a 14.0-mm diameter. A partial iridectomy and cryotherapy to the peripheral cornea and the angle were also performed. At the time of surgery the polypropylene suture loops were cut externally, and the lens was noted to fall back immediately into the vitreous cavity. Tying forceps were used to retrieve the lens. On gross examination, no fibrous tissue was noted on either haptic or suture. The patient had persistent increased intraocular pressures and regrowth of an epithelial sheet over the cornea and residual iris. Despite repeat penetrating keratoplasty, total iridectomy, peripheral cryotherapy, and endolaser to the ciliary body, the patient had persistent epithelial downgrowth, increased intraocular pressures, and subsequently developed phthisis.
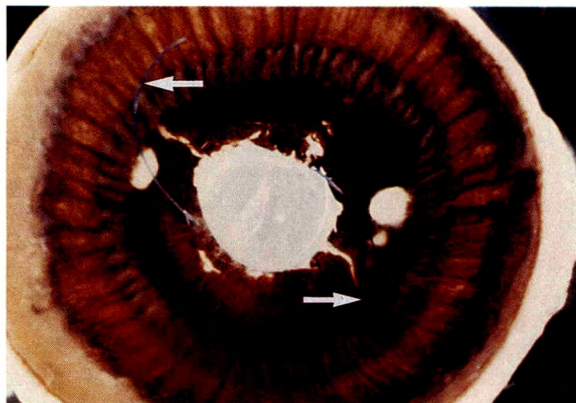
Fig. 1 (Lubniewski and associates). Case 1. Left, The eye from behind a three-piece modified C-loop posterior chamber intraocular lens. The haptics were oriented in the 8 o'clock to 2 o'clock axis at the time of surgery (arrows). The 8 o'clock haptic is positioned in the sulcus and is obscured by lens cortical remnants. The tip of the 2 o'clock haptic is suspended 2.0 mm posterior to the sulcus. Both sutures have been passed through the ciliary sulcus. Suture attachment to haptics is illustrated by white arrows ($\times 6.1$). Right, Magnified view of the 2 o'clock haptic showing successful sulcus placement of the suture without corresponding haptic placement. Note that the suture has been wrapped inadvertently around the haptic during insertion so that it is more proximally attached to the haptic than was intended ($\times 10.9$).
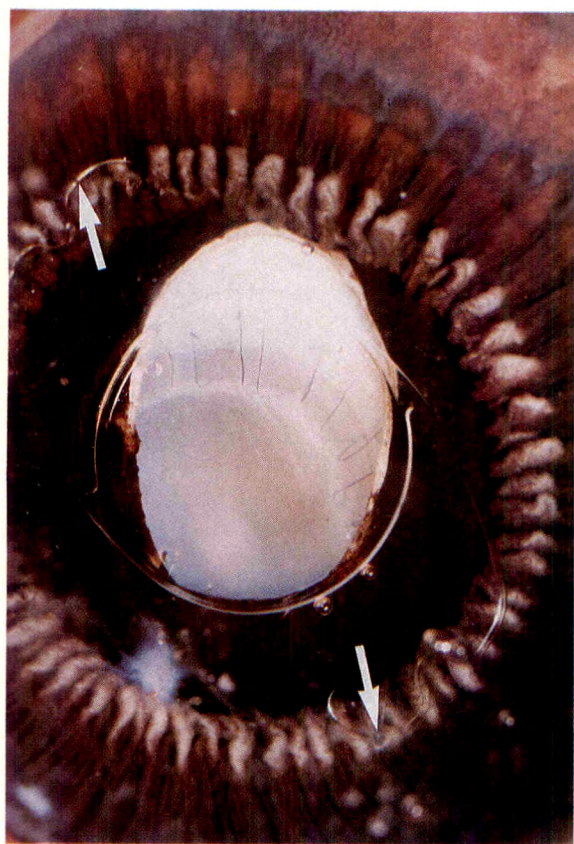
Fig. 2 (Lubniewski and associates). Case 2. The eye from behind a Bechert-style posterior chamber intraocular lens. A superior sector iridectomy is present. The haptics at the 8 o'clock and 2 o'clock meridians are attached firmly 1.0 mm posterior to the ciliary sulcus (white arrows). Both 10-0 polypropylene sutures are located between the positioning notch and the positioning hole at the haptic tip. No gross fibrosis is visible around either haptics or sutures six months postoperatively ($\times$ 8.7).

Results

In Case 1, the polypropylene sutures were noted externally under partial-thickness scleral flaps 1.0 mm posterior to the surgical corneoscleral limbus at the 8 o'clock and 2 o'clock meridians. The lens position was examined after the globe was opened coronally. The 8 o'clock haptic was attached to the ciliary sulcus by the polypropylene suture. The 2 o'clock suture passed through the ciliary sulcus, but the tip of the haptic was noted 2.0 mm posterior to the ciliary sulcus (Fig. 1, left). The 2 o'clock haptic was suspended on the ciliary body by the

suture, which had been wrapped around the distal haptic during insertion (Fig. 1, right). Results of histologic examination showed no inflammatory infiltrate surrounding the polypropylene suture as it passed through the sclera.

On external examination in Case 2, the polypropylene sutures at the 8 o'clock and 2 o'clock meridians were 1.9 and 2.2 mm from the surgical corneoscleral limbus. After opening the globe, each haptic was found securely attached approximately 1.0 mm posterior to the ciliary sulcus. The sutures were found in their original positions between the positioning hole and notch on each haptic. There was no gross fibrosis surrounding the haptic, suture, or adjacent ciliary body. No distortion of the globe or iris was noted. A superior sector iridectomy was present (Fig. 2). Results of a histologic examination of the section through the 8 o'clock haptic disclosed a thin fibrous capsule outlining where the haptic, which had dissolved during routine histologic processing, had been (Fig. 3, left). No acute or chronic inflammatory cells were noted around the suture as it passed through a ciliary body process (Fig. 3, right) and the sclera. Externally, the knot was well covered by conjunctiva. A moderate number of chronic nongranulomatous inflammatory cells were noted in the substantia propria and episclera surrounding the knot (Fig. 4, left). The tip of the polypropylene suture extended above the conjunctival surface (Fig. 4, right).

Discussion

Increased clinical experience with transsclerally sutured posterior chamber lenses indicates they are well tolerated in the eye.[3-8] Our histologic studies support this conclusion. In our first case, no inflammatory cells were seen around the transscleral portion of the suture. In our second case, no inflammatory cells were associated with the suture as it passed through the ciliary body and sclera. A delicate fibrous capsule surrounded the haptic at its attachment site to the ciliary body six months postoperatively.

Placement of the haptics in the ciliary sulcus may provide needed support for transsclerally sutured lenses, particularly if the suture is removed. The transscleral suture loop may be cut inadvertently when managing an exposed suture tip, or their removal may be intended.[6,7,16]
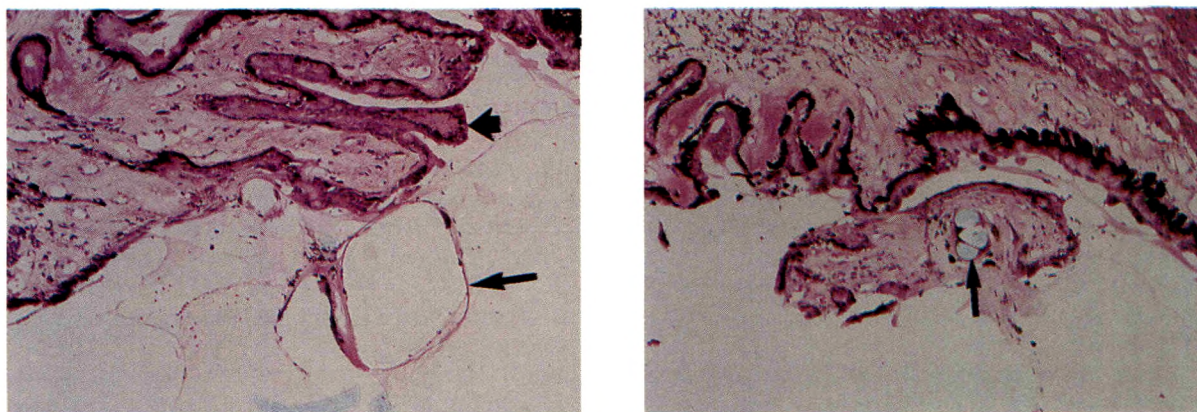
Fig. 3 (Lubniewski and associates). Case 2. Left, Photomicrograph through the attachment site of the lens haptic to the ciliary body at the 8 o'clock meridian. A delicate fibrous capsule (long arrow) outlines the position of the polymethylmethacrylate lens haptic that has dissolved during routine histologic preparation. No inflammatory cells are seen in adjacent ciliary body processes (short arrow) (×100). Right, Photomicrograph of the transscleral suture (arrow) as it passes through a ciliary body process. There are no inflammatory cells in the ciliary body process or adjacent ciliary body (×100).

Transsclerally sutured lenses presumed to be placed in the sulcus may remain in position after removal of all fixation sutures three to four months postoperatively.[7] Whether residual capsular flaps, haptic positioning in the sulcus, or fibrosis to the ciliary body played any role in these cases is unknown, since postmortem and histologic specimens were not available for examination. Dislocation of a transsclerally sutured lens that had been positioned on anterior pars plana has been reported four months after removal of one of two fixation sutures.[16]

Current surgical techniques do not guarantee ciliary sulcus placement of the haptic. In the histologic study of iris sutured lenses of Apple and associates,[15] seven of eight haptics were found posterior to the ciliary sulcus despite the clinical impression that they had been placed there. Our findings with transsclerally sutured lenses show that all three operating surgeons did not assess accurately the final location of the suture or haptics. In the first case, both fixation sutures were passed through the ciliary sulcus, although only one haptic was correctly positioned there. In the second case, both sutures were found 1.0 mm posterior to the ciliary sulcus and exited externally 2.0 mm posterior to the surgical corneoscleral limbus. Duffey and associates[17] have shown in work with cadaver eyes that sutures should be placed 0.83 mm
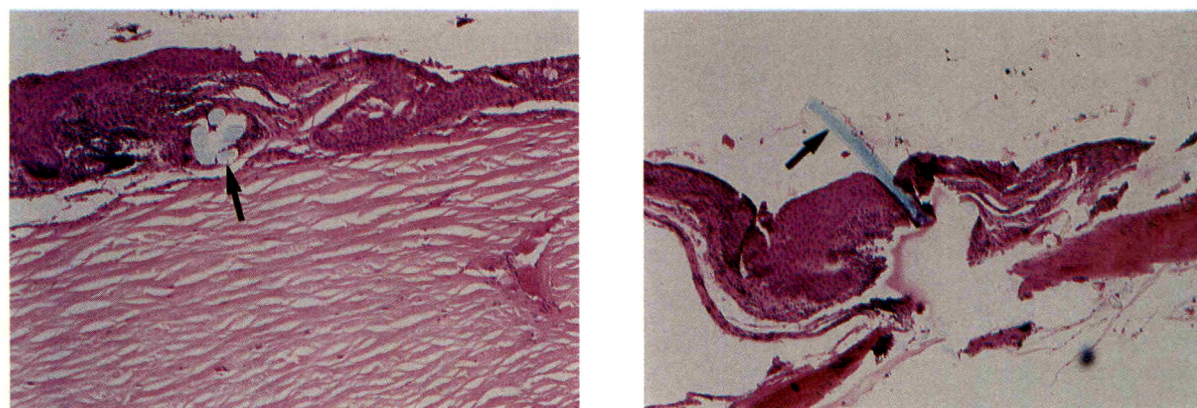
Fig. 4 (Lubniewski and associates). Case 2. Left, Photomicrograph of the external suture shows the knot has been well covered by conjunctiva. A moderate number of chronic nongranulomatous inflammatory cells are seen in the substantia propria and episclera surrounding the suture (arrow) (×100). Right, The tip of the polypropylene suture (arrow) extends through the conjunctiva onto the surface (×100).

vertically and 0.46 mm horizontally behind the surgical corneoscleral limbus to improve the chance of sulcus placement. In our third case, the intraocular lens fell back after removal of the transscleral sutures, presumably because the haptics were not supported by sulcus placement of haptics, fibrosis of haptics to ciliary body, or residual capsular flaps. Since there is no surgical technique to guarantee the haptic placement into the sulcus, we recommend leaving the transscleral suture in place to ensure lens stability.

Suture erosion to the conjunctival surface results in a potential route for epithelial downgrowth or infection. In our first two cases, no epithelial ingrowth was noted along the scleral suture track on histologic examination. In our third case, the clinically diagnosed epithelial downgrowth extending between the 11 o'clock and 3 o'clock meridians most likely resulted from an interrupted nylon suture leak at the 12 o'clock meridian. The transscleral sutures were at the 3 o'clock and 9 o'clock meridians, away from the area of downgrowth. Two cases of endophthalmitis have been reported with transsclerally sutured posterior chamber lenses.[16,18] In one case, a 9-0 polypropylene suture knot had eroded through a partial-thickness scleral flap and overlying conjunctiva six years postoperatively.[18] In the other case, a 9-0 polypropylene suture knot eroded through a conjunctival flap five months postoperatively.[16]

Erosion of 10-0 polypropylene knots, loops, and suture tips through both scleral and conjunctival flaps can occur at any time postoperatively[6,7] and has been seen by us in our clinical practices. In our second case, the knot was well covered at the three-month visit, but a suture tip was found to be exposed on postmortem examination six months postoperatively. Careful postoperative examination and removal of exposed suture tips by cautery may prevent this potential route for epithelial cells or infection. We have not removed any transscleral sutures for treating persistently exposed sutures. We prefer revising the conjunctival flap with placement of donor sclera over the exposed suture.

Strategies used at the time of surgery to minimize the chance of suture exposure include covering the sutures with conjunctival or scleral flaps. Techniques that may further reduce the risk of erosion of the fixation suture include tunneling the suture posteriorly in episclera before tying.[3,9] Cutting suture ends close to the knot may still leave suture barbs that can protrude. Application of a variable temperature

cautery on the lowest setting at the time of surgery has been successful in melting suture tips down to the knot, which is then covered by conjunctiva (Richard L. Lindstrom, M.D., oral communication, October 1989). We currently place sutures 0.75 mm posterior to surgical corneoscleral limbus under a 3.0-mm triangular partial-thickness scleral flap. The suture is tied to itself with the small loop and the suture end with the needle tunneled 2.0 to 3.0 mm posteriorly through the partial-thickness sclera, then cut flush with the surface as it exits the sclera.

The technique of transsclerally sutured posterior intraocular lenses continues to evolve. Our findings demonstrate that lens stability was derived primarily from the transscleral suture and not fibrous encapsulation, ciliary sulcus placement of lens haptics, or residual capsular flaps. Haptic positioning in the ciliary sulcus can be important for lens stability, although current techniques do not guarantee correct placement. Leaving transscleral sutures in place and surgical and postoperative efforts to minimize surface erosion of the suture tips are recommended. Transscleral fixation of lenses provides one of the best alternatives available to rehabilitate eyes with extensive anterior synechiae or loss of iris tissue in patients who are contact lens–intolerant. It can also be useful during intraocular lens exchange or secondary lens implant with or without penetrating keratoplasty. As clinical experience increases, the safety and efficacy of this procedure compared to iris sutured posterior lenses or flexible open-looped anterior chamber lens implants will become more clear.

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OPHTHALMIC MINIATURE

He stared, he snapped his fingers, his brow wrinkled deeply under the pushed-up glasses and the glasses fell down astride the flat bridge of his nose. They were odd glasses that in the sunlight refracted and divided the eyes behind them so that for an instant he looked as multiple-eyed as a horsefly. His mouth opened, and sure enough, there was the old wart on the end of his tongue. It pulled in and hid behind his lower teeth, it crept out again and lay slyly between his lips.

Wallace Stegner, *Angle of Repose*
New York, Fawcett Crest, 1972, p. 63

Reversible Visual Loss Caused by Fibrous Dysplasia

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and Harry V. Vinters, M.D.

Fibrous dysplasia is a developmental anomaly of bone, often affecting the facial bones. We treated a patient who had fibrous dysplasia involving the right maxillary and sphenoid bones. The patient had a sudden loss of visual acuity to R.E.: counting fingers. Visual fields demonstrated a central scotoma, and retrobulbar neuritis was diagnosed. When vision failed to improve spontaneously, however, radiologic studies were performed. These showed compromise of the optic canal by bony proliferation and an apparent mucocele at the orbital apex. Surgical exploration disclosed fibrous dysplastic bone and a cystic structure overlying the optic nerve. Successful surgical excision of the cyst and debulking of the fibrous dysplasia resulted in visual acuity returning to R.E.: 20/25.

FIBROUS DYSPLASIA is an abnormal development of bony tissue, which results in fibrous tissue proliferation and imperfect osteogenesis. This may produce facial deformity and asymmetry. Rarely, the abnormal bony proliferation may cause compression of adjacent structures with compromise of normal function. We treated a patient in whom fibrous dysplasia involving the sphenoid bone with a secondary mucocele resulted in compressive atrophy of the optic nerve at the orbital apex, which produced visual loss.

Case Report

A 29-year-old woman had right-sided fibrous dysplasia, which caused marked facial asymmetry. In 1982 the patient underwent removal of the floor of the right orbit as part of a procedure intended to improve cosmesis. Visual acuity remained R.E.: 20/20 after the operation. In March 1985, the patient had a sudden, severe, right-sided headache, retrobulbar in location. There was pain on versions to the right and decrease in visual acuity to R.E.: counting fingers. A moderate relative afferent pupillary defect was noted on the affected side with a normal disk appearance. Goldmann visual field testing showed a dense central scotoma involving the central 20 degrees of vision in the right eye, with a normal field of vision in the left eye. A computed tomographic scan of the orbits showed extensive changes of fibrous dysplasia involving the right maxillary, ethmoid, and sphenoid bones. Asymmetry in the orbits with a 2-mm proptosis of the right globe was seen. No bony encroachment of the optic nerve was demonstrated. Retrobulbar neuritis was diagnosed, and the patient was given prednisone. Two months later, visual acuity had returned to R.E.: 20/20, with resolution of the afferent pupillary defect.

Over the ensuing two years, the patient did well without any other focal neurologic signs or symptoms. In June 1987, the patient again had an aching pain over the right temporal fossa associated with pain upon horizontal ductions of the right eye. One day after the onset of symptoms, she noted dimming of central vision in her right eye associated with poor color perception. Visual acuity deteriorated rapidly over the next 24 hours, so that the patient could only distinguish shapes but no detail or color with the right eye. Visual acuity was R.E.: counting fingers associated with an afferent pupillary defect. Generalized enlargement of the right side of the face was noted with propto-
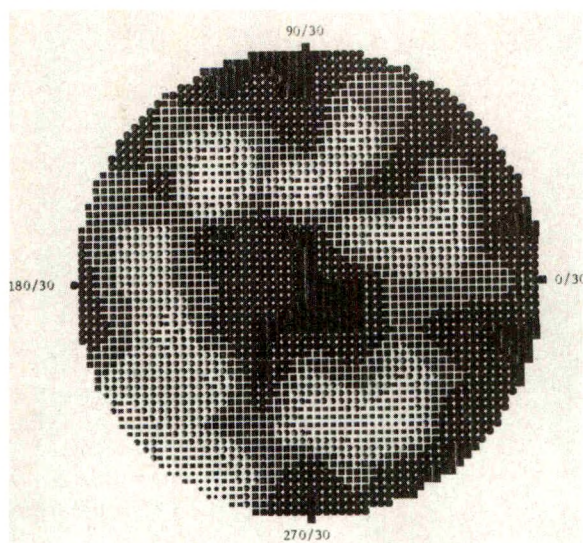
Fig. 1 (Weisman, Hepler, and Vinters). Preoperative visual field of the right eye demonstrating large central scotoma.

Fig. 2 (Weisman, Hepler, and Vinters). Axial computed tomographic scan of head showing fibrous dysplastic bone obliterating the right optic canal and a cystic lesion in the area of the right orbital apex.

sis and exophthalmometry readings of R.E.: 21.5 and L.E.: 19.5. The appearance of both optic disks was normal. Visual fields documented a central scotoma in the right eye involving the central 20 degrees with a markedly reduced sensitivity of all surrounding isopters (Fig. 1). We believed that this represented a recurrence of the retrobulbar neuritis, and the patient was treated with prednisone, 60 mg per day. Over the ensuing three weeks, however, visual acuity did not improve. A repeat computed tomographic scan showed extension of the fibrous dysplasia involving the sphenoid bone. This dysplastic bone appeared to fill the right optic canal, and a cystic structure originating from the sphenoid sinus, which probably represented a mucocele, was noted at the orbital apex (Fig. 2). A magnetic resonance image confirmed the extensive compromise of the right optic canal. Because of these findings, neurosurgical consultation was obtained. Computed tomography and magnetic resonance imaging findings were considered highly suggestive of compression of the right optic nerve within the optic canal, most likely caused by involvement of the lesser wing of the sphenoid bone by fibrous dysplasia. The patient elected to undergo neurosurgical exploration.

In July 1987, a right frontotemporal craniotomy was performed. Bone was significantly overgrown in the temporal region, particularly in the right sphenoid wing. A rongeur was used to remove this bony overgrowth. Material sent for permanent sections confirmed the diagnosis of fibrous dysplasia (Figs. 3 and 4). Dissection was extended medially toward the right orbital apex, where a cystic space was found to overlie the right optic nerve and replace the right anterior clinoid process. The dura mater overlying the right optic nerve was incised. This maneuver resulted in direct entry into the cystic cavity. The contents of the cystic area consisted of a shaggy, brown-green material. The operating surgeon believed that this cystic structure represented a mucocele. The cystic contents were excised completely, and the dural incision extended anteriorly along the course of the optic nerve. Soft fibrous dysplastic bone pressed upon the nerve medially. Abnormal bone was removed with a curette to achieve decompression of the nerve throughout its orbital course to the point of its entry into the dura mater. The lateral and superior borders of the right optic nerve were then inspected thoroughly, and no evidence of additional compression was found. At the end of the procedure, the right optic nerve was believed to be decompressed completely. The patient tolerated the procedure well without complications.

On the fourth postoperative day, the patient noted that her vision had improved, compared with her preoperative status. Best-corrected visual acuity was R.E.: 20/300. The afferent pupillary defect persisted. The ophthalmoscopic appearance was unchanged. The patient continued to do well and was discharged on the sixth postoperative day.
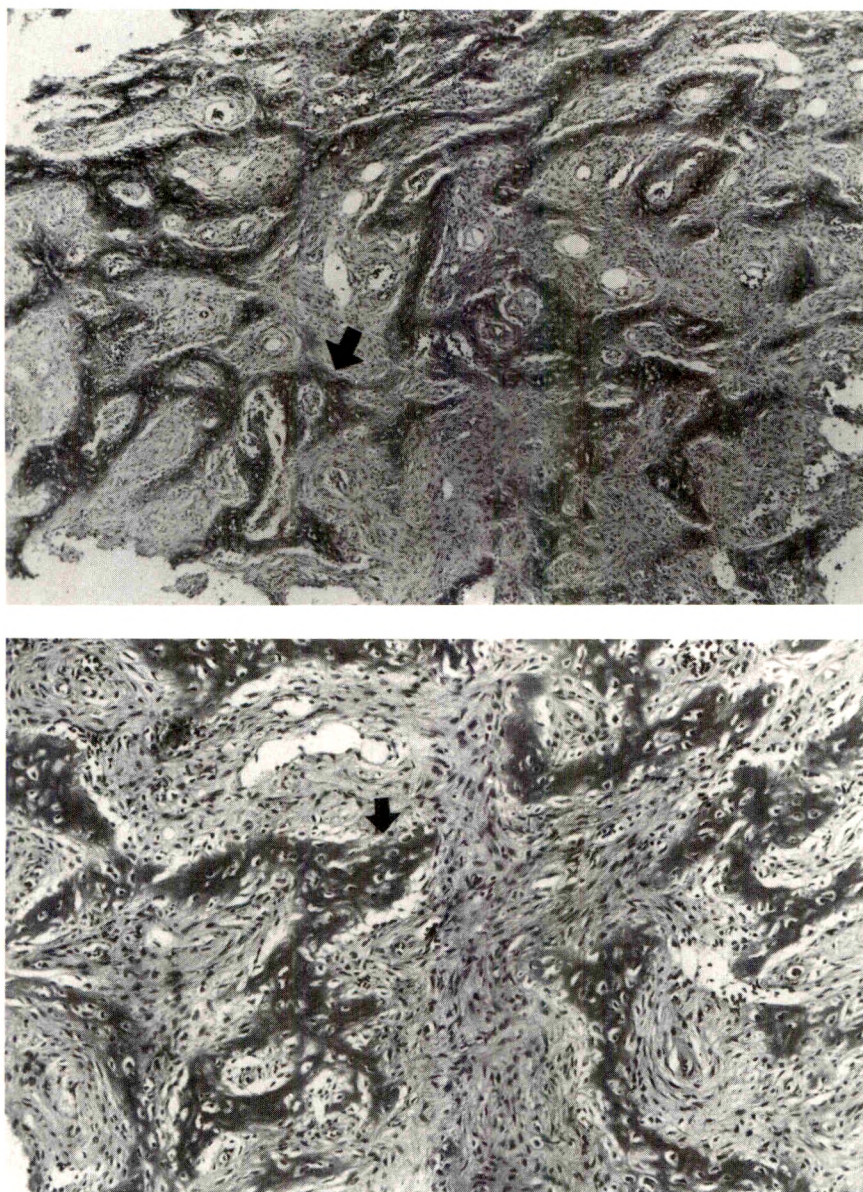
Fig. 3 (Weisman, Hepler, and Vinters). Sections of the surgically resected material photographed at low (top) and high (bottom) magnification show large amounts of fibrous connective tissue separating islands of woven bone (arrows). Cells within the fibrous component show uniform nuclei without mitotic figures (bottom). The bone shows prominent osteocytes but scant osteoblast or osteoclast activity (hematoxylin and eosin; top, × 76; bottom, × 190).

Re-examination six weeks postoperatively demonstrated improvement of visual acuity to R.E.: 20/25^{+2}. A trace afferent pupillary defect persisted, and mild temporal pallor was seen in the optic nerve head. Repeat visual fields demonstrated complete resolution of the central scotoma (Fig. 5).

In June 1990, the patient had sudden right periorbital pain and visual loss. Computed tomographic scans demonstrated recurrence of mucocele compressing the right optic nerve. An emergency craniotomy confirmed the scan findings, and the mucocele was evacuated. The patient noted immediate restoration of nearly all of her vision one day after the craniotomy.

Discussion

Fibrous dysplasia is a developmental abnormality of bone in which normal bone is replaced gradually by fibrous tissue. This process occurs primarily during childhood, although

Fig. 4 (Weisman, Hepler, and Vinters). Sections of surgical specimen viewed under polarized light show disorganized nature of the coarse woven bone (top), compared with the organized pattern identified in an adjacent normal fragment of bone (bottom) (hematoxylin and eosin, ×76).

progression may continue into adulthood. Chen and Fairholm[1] reported that fibrous dysplasia may progress during adult life, and that optic nerve function may be impaired if the orbital sphenoid bone is involved. In 1984, Sevel and associates[2] reported a case in which sudden enlargement of an area of fibrous dysplasia caused by a hemorrhage in its substance resulted in compression of the optic nerve and consequent reduction of visual acuity to light perception. In their patient, surgical removal of the tumor mass enabled return of visual acuity to $20/20^{-3}$. Donoso, Magargal, and Eiferman[3] described a 13-year-old girl in whom constriction of the optic canal caused by fibrous dysplasia of the lesser wing of the sphenoid accounted
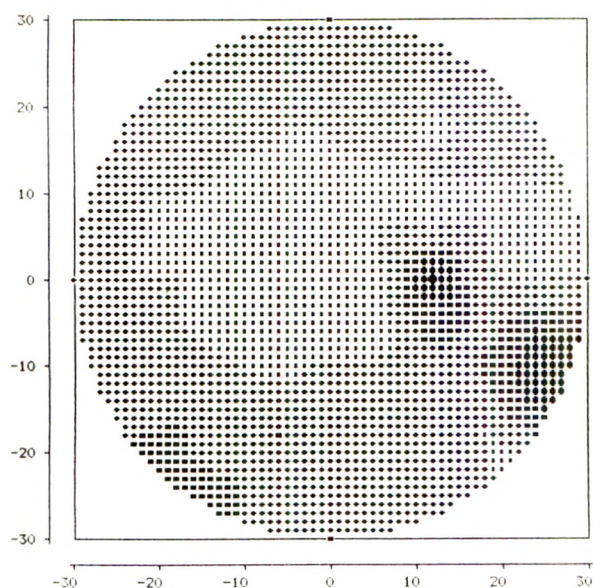
Fig. 5 (Weisman, Hepler, and Vinters). Visual field of the right eye six weeks postoperatively showing resolution of the central scotoma.

for optic atrophy with visual acuity of 20/80. In this patient, decompression failed to improve vision; however, marked pallor of the nerve had been noted preoperatively. In 1985, Moore, Buncic, and Munro[4] reported 16 cases of orbitocranial fibrous dysplasia in children. Five of these children had radiologic evidence of narrowing of the optic canal; within this group, two developed optic atrophy and visual loss.

There are two types of fibrous dysplasia: monostotic, which involves primarily a single bone or contiguous bones; and polyostotic, which involves multiple bones at different sites.[5] Most patients with disease involving the orbit have the monostotic form. If the sphenoid bone is involved, compromise of the optic canal with compressive optic atrophy may result. In our patient, fibrous dysplasia involving the sphenoid bone led to the development of a sphenoidal mucocele. The fibrous dysplasia and secondary cyst caused marked narrowing of the optic canal with subsequent optic atrophy and visual loss. Successful surgical decompression led to excellent recovery of vision.

The radiologic features of fibrous dysplasia involving the orbit have been reported.[4] On plain films, the lesions may be lytic, sclerotic, or both. A ground glass appearance has been described in affected areas. These lesions may be mistaken for other entities such as en plaque

meningioma, Paget's disease, or bone cyst. Computed tomography and magnetic resonance imaging may be used to differentiate these entities and to define more precisely the boundaries and extent of involvement of the lesion.

On histopathologic examination, the major change is fibrous tissue replacement of the medullary centers of bone. Cells sometimes arrange concentrically around a zone of developing cartilage. Small islands of poorly calcified bone, as well as irregular trabeculae of bone with attached fibrous tissue, may be found.[5] The term, "immature woven bone," has been used widely by ophthalmologists to describe the overall microscopic appearance of these specimens. The fibro-osseous proliferative tissue is highly vascular and causes extensive, dispersed, low-flow bleeding when surgically excised. The inner surface of bone cortex surrounding these areas of fibrous proliferation may become eroded as the disease progresses, but the outer surface of the cortex remains intact.[5] In our patient, two classic histologic characteristics of fibrous dysplasia were seen. First, there were many fibroblasts with accompanying fibrovascular proliferation between the bony lamellae. Additionally there were multiple pockets of immature, woven bone.

Several ocular complications have been reported in association with fibrous dysplasia. These include proptosis and secondary exposure keratitis, restriction of motility with resultant diplopia, blepharoptosis, epiphora, and visual field loss.[4,5] When the orbital maxilla is involved, the globe is pushed upward; if the orbital roof is involved, as in our patient, hypoglobus occurs. If the eye has been displaced for many years, a dull aching pain may occur around the orbit.[5] Involvement of the sphenoid bone with fibrous dysplasia may lead to compromise of the optic canal. This process may lead physicians to conclude erroneously that a meningioma is present; however, the degree of facial asymmetry seen with fibrous dysplasia is rarely seen with meningiomas. When visual loss occurs from compression of the optic nerve, surgical decompression should be undertaken promptly, as some of the atrophic changes may be reversible in their early stages.

The origin of this disease is not clearly understood. Possibly, it involves a defect in the bone-forming mesenchyme.[3] The disease is usually most active during the second and third decades, when growth maturation occurs. No cases

of malignant transformation of orbital fibrous dysplasia have been reported.[5]

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OPHTHALMIC MINIATURE

If there ever was a justification for the Bastille, it was the Marquis de Sade. But if the crimes which put him there were unusually disgusting (by the standards of any century), his living conditions were not. He received visits from his long-suffering wife almost weekly and when his eyes deteriorated from both reading and writing, oculists came to see him on a regular basis. Like others in the "Liberty" tower, he could walk in the walled garden courtyard and on the towers. Only when he abused that right by shouting cheerful or indignant obscenities to passersby (which he did with increasing frequency in 1789) was it curtailed.

Simon Schama, *Citizens*
New York, Alfred Knopf, 1989, pp. 391-392

Management of Subretinal Foreign Bodies With a Cannulated Extrusion Needle

Brian C. Joondeph, M.D., and Harry W. Flynn, Jr., M.D.

We treated two patients who had nonmagnetic subretinal foreign bodies (metallic pellet and lens nucleus fragment) in the presence of a retinal detachment and a distant retinal break. After the pars plana vitrectomy, the soft, flexible tip of the cannulated extrusion needle was used to push the foreign object gently away from the posterior pole toward the retinal break where it was grasped and removed from the eye. This technique for subretinal foreign body removal is preferable to creating a large posterior retinotomy overlying the foreign body because of the potential risks of further macular trauma, hemorrhage, or proliferation of periretinal membranes from the retinotomy site.

DESPITE RECENT ADVANCES in vitreous microsurgery, the surgical management of posterior intraretinal and subretinal foreign bodies remains difficult.[1,2] Although anteriorly located foreign bodies can be removed externally through a scleral incision, posteriorly located foreign bodies in the subretinal space may require a retinotomy over the object to remove it. We treated two patients (one with a subretinal foreign body in the macula and the other with a subretinal lens nucleus fragment adjacent to the optic disk) by using a cannulated extrusion needle[3] that enabled removal of the foreign material without creation of a posterior retinotomy.

Case Reports

Case 1

A 15-year-old boy was shot with a pellet gun and sustained a scleral perforation in the left eye. A computed tomographic scan disclosed the presence of a single intraocular foreign body embedded in the posterior wall of the eye (Fig. 1). Nine days after primary repair of the scleral perforation, visual acuity was L.E.: 3/200. The patient also had an early cataract with mild vitreous hemorrhage, a poorly visualized foreign body in the posterior pole, and an inferior retinal detachment confirmed by echography.

A pars plana lensectomy and a vitrectomy were performed, which showed a 3-mm metallic foreign body in the subretinal space near the
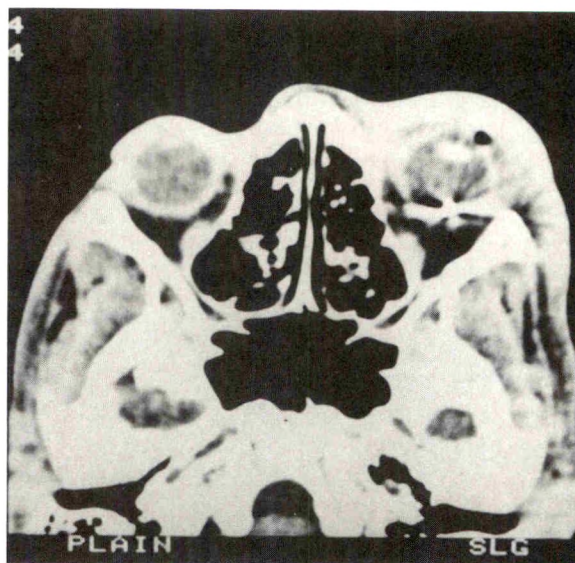
Fig. 1 (Joondeph and Flynn). Case 1. Computed tomographic scan demonstrating a metallic intraocular foreign body embedded in the posterior wall of the left eye.
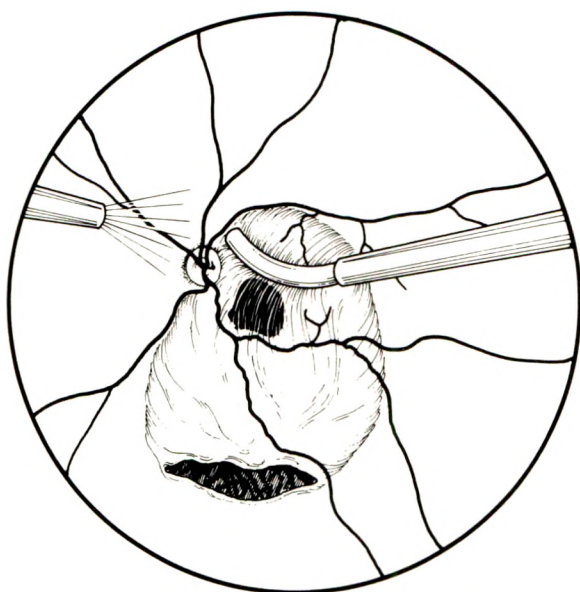
Fig. 2 (Joondeph and Flynn). The partially extended, soft silicone tip of the cannulated extrusion needle is used to push the foreign body gently away from the posterior pole toward the retinal break.
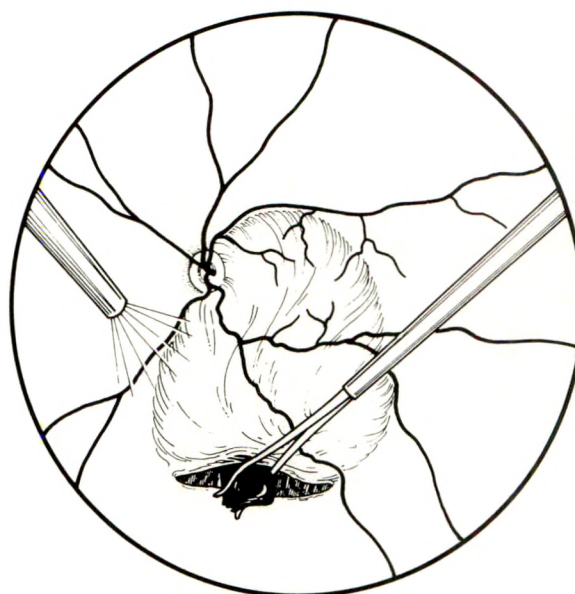
Fig. 3 (Joondeph and Flynn). The foreign body is then grasped with intraocular foreign body forceps and removed from the eye. An intraocular magnet could also be used if the foreign body is magnetic.

center of the macula. The retina was detached in this area, and the detachment extended inferiorly to a linear retinal tear at the inferotemporal equator, where the foreign body presumably entered the subretinal space. There was also a retinal laceration in the temporal periphery underlying the scleral perforation site. Attempts to reach the pellet through the inferior retinal break by using foreign body forceps were unsuccessful, and there was a risk of further tearing of the retina. Magnetic extraction was not possible since the pellet was nonmagnetic.

Removal of the pellet was then attempted by using the cannulated extrusion needle with the soft silicone cannula extended to approximately 8 mm beyond the metal shaft. The retina was brushed with the soft cannula (Fig. 2), and the pellet was pushed toward the inferior retinal break where it was eventually grasped with the foreign body forceps (Fig. 3) and removed through an enlarged pars plana sclerotomy. Even though there was pigment disruption in the subretinal space caused by pushing the pellet along the pigment epithelium, there were no subretinal hemorrhages or breaks in the overlying retina. A fluid-gas exchange was then performed, which drained subretinal fluid internally by using the cannulated extrusion nee-

dle (Fig. 4). Argon laser endophotocoagulation was placed around the retinal break (Fig. 5), and an encircling scleral buckle was placed at the equator.

Two months after the vitrectomy, the patient's retina remained attached and visual acuity was L.E.: 20/200 with aphakic correction. Mild subretinal fibrosis near the macula has developed (Fig. 6).

Case 2

A 48-year-old woman with a recurrent retinal detachment and proliferative vitreoretinopathy Grade C2 (star folds in inferior quadrants) in the left eye was found to have a large retinal tear at the 6 o'clock meridian posterior to a previously placed scleral buckle. During the pars plana lensectomy, a substantial portion of the lens nucleus fell posteriorly. The nucleus entered the subretinal space through the inferior retinal break and settled adjacent to the inferior pole of the optic disk. After completion of the vitrectomy and epiretinal membrane resection, the cannulated extrusion needle was used to push the nuclear fragment gently away from the disk toward the inferior retinal break. The nucleus was then aspirated into the lens fragmentation needle and removed from the eye. A fluid-gas exchange was performed to
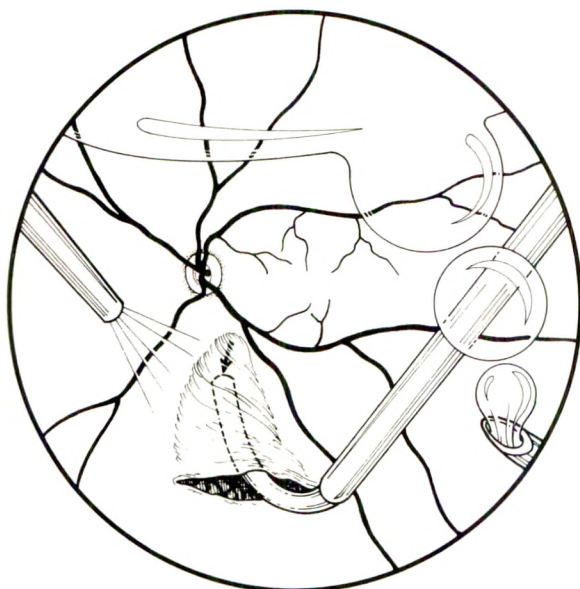
Fig. 4 (Joondeph and Flynn). A fluid-gas exchange is then performed to reattach the retina, draining subretinal fluid internally through the pre-existing retinal break by using the cannulated extrusion needle.
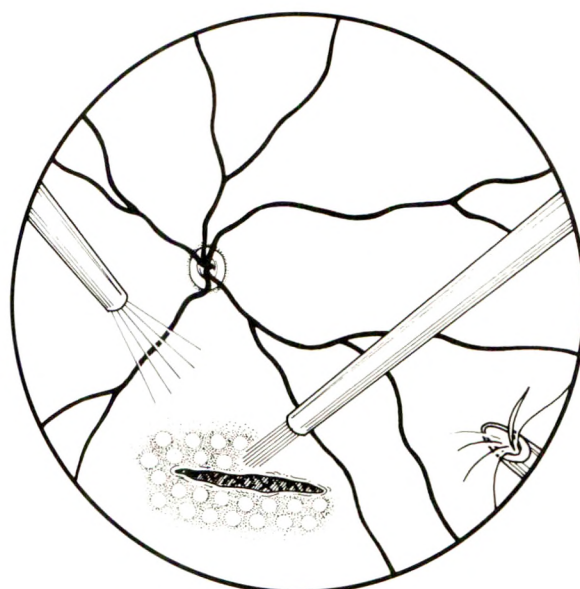
Fig. 5 (Joondeph and Flynn). Laser endophotocoagulation is then placed around the retinal break.

achieve retinal reattachment, and argon laser endophotocoagulation was placed around the break.

Two months postoperatively, the inferior retina redetached, and repeat pars plana vitrectomy, epiretinal membrane peeling, fluid-gas exchange, and argon laser endophotocoagulation were performed. After six months of follow-up from this operation, the retina remained attached with 20/400 visual acuity in the affected eye.

Discussion

Slusher, Sarin, and Federman[1] described an approach to the management of intraretinal foreign bodies by using pars plana vitrectomy and foreign body extraction with intraocular forceps through the pars plana. None of their cases involved subretinal foreign bodies in the posterior pole, as we encountered. Although they were able to remove the foreign body in all 14 cases, they noted a 90% incidence of macular pucker, subretinal fibrosis, or proliferative vitreoretinopathy postoperatively.

Creation of a posterior drainage retinotomy has been associated with proliferation of preretinal membranes, which causes macular traction and recurrent retinal detachment.[4] An alternative method for internal drainage of subretinal fluid uses the pre-existing peripheral retinal break and a cannulated extrusion needle.[3] The cannulated extrusion needle has an extendable 18-mm soft silicone cannula, which is also useful in the surgical management of giant retinal tears, that can be used to push or pull the retina anteriorly to correct posterior slippage.[5]

The silicone tubing was used to push the subretinal foreign body in our cases. The softness and flexibility of the needle's silicone tubing allowed delivery of the subretinal foreign body to the pre-existing break without causing an additional retinal break in or near the macula. This technique has advantages over creation of a retinotomy overlying the foreign body in the macular region, in that it avoids further posterior retinal damage and the potential for late cellular proliferation from the retinotomy.

Lewis and associates[6] described nine patients with retinal tack intrusion, three of which were retained in the subretinal space. In two of the three eyes, the tacks were not removed either because the retina could be reattached over the tacks with good potential vision or because the poor visual prognosis did not warrant further
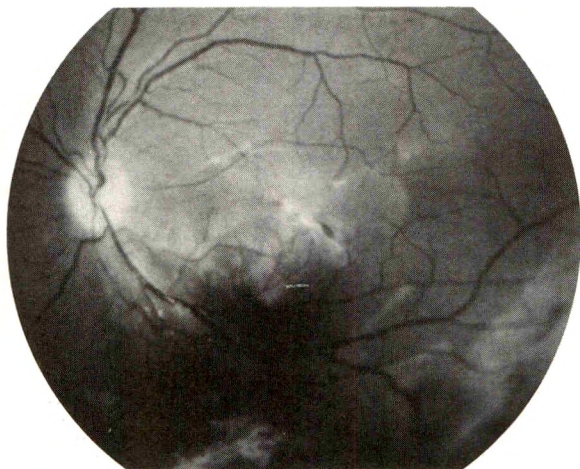
Fig. 6 (Joondeph and Flynn). Case 1. Fundus appearance two months postoperatively. There is scarring around the retinal break in the inferotemporal quadrant.

intervention. In the one remaining case, the tack was removed with intraocular forceps, although the technical details were not described. The authors reported that the indications for removing subretinal tacks were a freely mobile tack under the macula or posterior pole, which caused retinal pigment epithelial and photoreceptor disruption and inflammation. These indications apply equally well to other subretinal foreign bodies, including our cases of nonmagnetic pellet and lens nucleus fragment.

A patient with a subretinal lens nucleus after successful repair of retinal dialysis by lensectomy and vitrectomy attained improved vision even with the nucleus retained in the subretinal space.[7] Despite this successful case, we believe that the inflammation induced by subretinal foreign bodies in the posterior pole may cause a significant visual loss and that these foreign bodies should be removed when possible.

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Ophthalmic miniature
Stephen Hill had romantic good looks, with very pale skin and lustrous raven hair, and with moist brown eyes that offered more sympathy than anyone, including himself, could hope to deliver.
Louis Auchincloss, *The Lady of Situations*
New York, Houghton Mifflin, 1990, p. 91

Needle Revision With and Without 5-Fluorouracil for the Treatment of Failed Filtering Blebs

Robert H. Ewing, M.D., and Robert L. Stamper, M.D.

Twelve patients with failed or failing filtering blebs were treated by transconjunctival needle revision of the bleb. Seven of these received 5-fluorouracil as an adjunct. Intraocular pressure decreased from 31.3 ± 8.8 mm Hg (range, 20 to 47 mm Hg) to 17.0 ± 3.7 mm Hg (range, 8 to 22 mm Hg). The length of follow-up ranged from two to 31 months. The results in 11 of 12 patients (91.6%) were satisfactory, defined by an intraocular pressure of 22 mm Hg or less, with or without antiglaucoma medications, and requiring no subsequent procedures for control of intraocular pressure. The success rates and overall pressure lowering effect of the seven patients receiving and the five patients not receiving 5-fluorouracil were similar. However, most patients receiving 5-fluorouracil were thought to be at higher risk for surgical failure. Complications of needle revision were minor and resolved without sequelae. We advocate the consideration of transconjunctival needle revision with or without the use of 5-fluorouracil as a useful therapeutic modality in the management of the failed or failing filtering bleb.

FAILURE OF THE FILTERING BLEB is a serious problem that occurs at various times after glaucoma filtering surgery. As the external aqueous drainage declines, the intraocular pressure may return to a level sufficient to produce optic nerve damage. Bleb failure is more frequent in complicated clinical situations such as those involving previous failed filtering surgery, other surgery involving conjunctiva,[1] or in certain secondary glaucomas.[2]

The management of the failing or failed bleb is difficult and many approaches have been proposed. Revision of a preexisting filtering site has several theoretic benefits: it preserves conjunctiva, is essentially an extraocular procedure, does not require the implantation of foreign materials, and does not damage the ciliary body. Needle revision of a failed or failing filtering bleb, especially in the management of an encapsulated filtration bleb, has been favorably described by several authors.[3-8] It has the additional advantage, compared to surgical revision, of a much smaller conjunctival incision, and may therefore incite less postoperative fibrosis as it heals. It would also be less likely to leak to the conjunctival surface postoperatively, an important consideration if 5-fluorouracil is to be used as an adjunct.

The use of postoperative subconjunctival 5-fluorouracil has been shown to increase the surgical success rate for eyes that have had previous surgery and undergone subsequent trabeculectomy.[9] This information led us to investigate needle revision of failed filtering blebs with and without the postoperative use of 5-fluorouracil.

Patients and Methods

Patient selection—The records of 12 patients who underwent needle revision for a failed or failing filtering operation with excessive intraocular pressures were reviewed. Patients with previously successful filtration surgery were considered candidates for needle revision if their intraocular pressures exceeded that level likely to damage the optic nerve further. One

additional patient who underwent needle revision after filtering surgery was excluded from the study because of severe trauma, which resulted in phthisis bulbi thought not to be related to his glaucoma operations. The preoperative patient characteristics are listed in Table 1.

Patients were from referral glaucoma practices; earlier operations were often performed by referring physicians by using varying techniques. All patients had been treated with the maximally tolerated antiglaucoma medical regimen as well as appropriate laser surgical intervention.

The decision to perform needle revision was made if some filtration was present as evidenced by at least some evidence of a bleb and an open internal stoma. Some of the patients (six of 12) had no area of superior conjunctiva not involved from previous surgery and hence were thought to be at high risk for failure of repeat conventional surgery.

Clinical features—The bleb sites were variable in appearance. Some eyes showed a small, usually thin-walled bleb very near the filtration site seemingly limited in extent by episcleral fibrosis. Others were thicker, more diffuse, and usually very shallow. All blebs were specifically differentiated from the bleb type known as an encapsulated bleb or Tenon's cyst, which is typically a localized, tense, and highly domed structure that develops in the early postoperative period.[10]

Eight patients had a single operative procedure before needle revision. Four patients had undergone from two to four previous procedures.

Multiple needle revisions were sometimes required. Five patients underwent more than one needle revision because of inadequate pressure control after the procedure.

The timing of needle revision relative to the antecedent filtering surgery was variable, needle revision being performed from two weeks to ten years after earlier surgeries.

5-Fluorouracil—As the benefits of 5-fluorouracil became apparent to us in routine filtering operations we began to use it in needle revision. Seven of the 12 patients received adjunctive 5-fluorouracil. Dosages ranged from six to 11 subconjunctival injections of 5 mg given over seven to 20 days. Patients with more numerous previous procedures tended to receive postoperative 5-fluorouracil more frequently than those with fewer previous procedures. Three of the five (60.0%) patients not receiving 5-fluorouracil had undergone only a single pre-

vious filtering operation. Only two of the seven (28.6%) patients receiving 5-fluorouracil had had such limited surgery.

Demographics—The patients ranged from 25 to 87 years in age. The diagnoses were mixed. Seven patients had primary open-angle glaucoma, two had normal tension glaucoma, two had secondary angle-closure glaucoma, and one had primary angle-closure glaucoma.

Procedures were considered a "success" if the intraocular pressure was 22 mm Hg or less without the use of antiglaucoma medications and no further operative procedures were required for glaucoma during the follow-up period. A "qualified success" was present if the intraocular pressure was maintained at 22 mm Hg or below with the aid of antiglaucoma medication and if no further operative intervention was required. A "failure" was present if the intraocular pressure was greater than 22 mm Hg despite medications or if further surgery to lower the intraocular pressure was required or planned.

Surgical technique—The procedure was performed in a minor surgery room under sterile conditions. Magnification with loupes or a microscope was used. Several doses of a broad-spectrum antibiotic eyedrop were given. The surrounding skin was cleaned with a 5% povidone-iodine solution and a drop of this mixture was placed into the eye. A plastic barrier drape was used and a wire eyelid speculum separated the eyelids. With the eye infraducted, the conjunctiva was anesthetized with topical 4% lidocaine applied by cotton swab. A ⅝-inch, 25-g disposable needle then punctured the conjunctiva approximately 10 mm from the preexisting bleb and 1% lidocaine containing 1:100,000 epinephrine to aid hemostasis was slowly injected, ballooning up the conjunctiva but taking care not to introduce the solution into the area of the scleral fistula.

The eye was stabilized by grasping conjunctiva near the entry site with forceps. The injecting needle was repeatedly advanced and withdrawn subconjunctivally keeping the tip near or on the scleral surface while puncturing the fibrous episcleral tissue. The bevel of the needle was directed toward the sclera to minimize the chance of puncturing the globe. When the tissue was sufficiently disrupted, the sharp lateral edges of the needle were used to sweep back and forth in a slicing manner further incising the scar. Care was taken not to buttonhole the conjunctiva or to enter the eye.

The eye would typically become soft during

TABLE 1
PREOPERATIVE PATIENT CHARACTERISTICS

PATIENT NO.	SEX	EYE	TYPE OF GLAUCOMA	RACE	AGE AT FINAL NEEDLE REVISION (YRS)	OPERATIVE PROCEDURES BEFORE FINAL NEEDLE REVISION	TIME BETWEEN PROCEDURE AND FINAL NEEDLE REVISION	5-FLUORO-URACIL DOSES BEFORE FINAL NEEDLE REVISION (5 MG)	5-FLUORO-URACIL DOSES AFTER FINAL NEEDLE REVISION (5 MG)
1	M	R.E.	Acute angle-closure	Hispanic	67	Trabeculectomy	6 wks	0	0
2	M	L.E.	Primary open-angle	White	72	Trabeculectomy	15 mo	0	0
3	M	R.E.	Primary open-angle	White	73	Full-thickness filter	3 mo	0	0
4	F	R.E.	Primary open-angle	Oriental	25	Trabeculectomy	24 mo	0	0
						Trabeculectomy	16 mo		
5	M	L.E.	Primary open-angle	White	71	Intracapsular cataract extraction with inadvertent bleb	10 yrs	0	0
						Needle revision	2 mo		
6	F	R.E.	Secondary angle-closure	Hispanic	60	Trabeculectomy	4 yrs		7
						Vitrectomy and lensectomy	24 mo		
						5-Fluorouracil trabeculectomy	11 mo	11	
						360-degree scleral buckle	9 mo		
						Prior needle revision	7 mo	8	
7	M	L.E.	Primary open-angle	White	87	Extracapsular cataract extraction, posterior chamber intraocular lens, trabeculectomy	18 mo	0	11
						Prior needle revision	2 mo		
8	M	L.E.	Primary open-angle	Oriental	72	Extracapsular cataract extraction, posterior chamber intraocular lens, trabeculectomy	8 mo		10
						Prior needle revision	1–5 mo	9 total	
9	F	L.E.	Normal-tension	White	48	Full-thickness filter	5 mo	0	7
10	M	L.E.	Normal-tension	White	64	Trabeculectomy	35 yrs		7
						Extracapsular cataract extraction, posterior chamber intraocular lens, full-thickness filter	10 mo		
						Needle revision	3 mo	8	
11	M	R.E.	Uveitic	White	59	5-Fluorouracil trabeculectomy	9 mo	5	6
12	F	R.E.	Secondary angle-closure	White	73	Extracapsular cataract extraction, posterior chamber intraocular lens	5 yrs	0	10
						Trabeculectomy	34 mo		
						Trabeculectomy	22 mo		
						Full-thickness filter	2 mo		

the procedure and an obvious bleb would form. When the episcleral scar was judged sufficiently disrupted the needle was withdrawn. The conjunctival wound was not closed. Additional antibiotic eyedrops were given, and the patient was instructed to continue them four times daily for 1 week.

Patients were examined the next day. If no conjunctival leak was present and 5-fluorouracil was to be given, a subconjunctival injection of 5-fluorouracil, 5 mg in 0.1 ml, was given inferiorly. Patients so treated were given six to ten injections usually over two weeks. Based on the appearance of the bleb, the number and timing of 5-fluorouracil injections were adjusted. Blebs showing signs of active fibrosis such as localization, thickening, or vascularization were given more frequent, usually daily, injections. If a frank epithelial defect developed the 5-fluorouracil was not given until reepithelialization ensued. Postoperative topical therapy was individualized but included prednisolone acetate 1% given every one or two hours for the first week, tapering over the next four weeks. Atropine 1% was usually given two to three times daily for the first week. Digital pressure was applied by the surgeon whenever the bleb was clinically believed to demonstrate signs of failure or when the pressure rose above 16 mm Hg.

Results

Follow-up ranged from two to 31 months with an average of nine months (Table 2). Intraocular pressure decreased from 31.3 ± 8.8 mm Hg (range, 20 to 47 mm Hg) to 17.0 ± 3.7 mm Hg (range, 8 to 22 mm Hg). Overall, seven of 12 (58.3%) patients achieved a successful result, four of 12 (33.3%) patients achieved a qualified success, and one of 12 (8.3%) did not achieve adequate control.

In the subgroup receiving 5-fluorouracil success was achieved in four of seven (85.7%) patients and qualified success was achieved in two of seven (28.6%) cases. In those not receiving 5-fluorouracil success was achieved in three of five (60.0%) patients and qualified success in two of five (40.0%) patients.

Five needle revisions were performed in one patient, the only failure. Four other patients required multiple needle revisions, all resulting in qualified successes. 5-Fluorouracil was ad-

ministered in four of the five repeat needlings. Success was achieved both with and without its usage. The number of previous operative procedures did not influence the ultimate success rate.

The interval between the primary operation and needle revision appeared to make little difference in outcome. Needle revision was done in the sole failure three months after his earlier filtering surgeries.

Complications were few and manageable. Most patients receiving 5-fluorouracil developed punctate staining and five of seven (71.4%) developed large corneal epithelial defects. All healed within three weeks with return of preoperative vision within eight weeks. One of these patients developed immediate shallowing of the anterior chamber and a small hyphema one day after the procedure, both of which resolved within two weeks. One patient had previously developed a large nonfunctioning overhanging bleb after trabeculectomy, which enlarged after needling and 5-fluorouracil. It was later excised with maintenance of pressure control. Two patients developed conjunctival leaks remote from the needle entry. The leaks closed spontaneously within ten days despite having received doses of 5-fluorouracil.

Discussion

The clinical options for the glaucoma patient with a failed filtering procedure are limited. Several approaches have been attempted. These include revision of the bleb, filtering stoma, or both, either surgically or with therapeutic ultrasound, disrupting the fibrotic bleb with the Nd:YAG laser,[11] creation of another filtering site away from the compromised one, placement of a glaucoma drainage implant, or a cyclodestructive procedure.

Subsequent filtering procedures are frequently more difficult to perform and have an increased rate of failure. Glaucoma drainage implants are useful in eyes with poor prognoses but require more expertise, have an increased incidence of complications, and expose the eye to the specific problems associated with implanted foreign materials. Cyclodestructive procedures are difficult to titrate accurately and carry a significant risk of complications, including visual loss and phthisis. Transconjunctival needle revision is a fairly simple technique to

TABLE 2
POSTOPERATIVE PATIENT CHARACTERISTICS

PATIENT NO.	SEX	EYE	LENGTH OF FOLLOW-UP (MO)	PRE-NEEDLE REVISION PRESSURE (MM HG)	FINAL PRESSURE (MM HG)	FINAL MEDICATIONS	POSTOPERATIVE EVENTS	FINAL RESULT
1	M	R.E.	31	28	17	None	Pendulous bleb requiring revision	Success
2	M	L.E.	16	40	18	Timolol	—	Qualified success
3	M	R.E.	2	22	11	None	—	Success
4	F	R.E.	16	47	19	None	—	Success
5	M	L.E.	5	34	22	(Refused)	—	Qualified success
6	F	R.E.	3	31	15	None	5-Fluorouracil related epithelial defect	Success
7	M	L.E.	6	44	22	Levobunolol, pilocarpine, massage	—	Qualified success
8	M	L.E.	13	31	21	Timolol, carbachol, methazolamide	5-Fluorouracil related epithelial defect	Failure (surgery planned)
9	F	L.E.	9	22	14	None	Hyphema 5-Fluorouracil related epithelial defect	Success
10	M	L.E.	4	20	15	Timolol, pilocarpine gel	Conjunctival leak 5-Fluorouracil related epithelial defect	Qualified success
11	M	R.E.	3	25.	18	None	Conjunctival leak	Success
12	F	R.E.	3	32	12	None	5-Fluorouracil related epithelial defect	Success

interrupt the subconjunctival scar and restore the bleb space. We have used it to enhance a return of aqueous drainage while minimizing surgical trauma.

Other authors have reported good results with various techniques of bleb rehabilitation. Cohen and associates[8] were able to restore function to failed blebs in 14 of 16 patients using an open revision with concomitant repair of the sclerostomy site. In a different group of patients, needle revision was successful in nine of 15 attempts. Yablonski and associates[12] restored 15 of 20 nonfunctioning blebs with therapeutic ultrasound. Encapsulated filtering blebs were successfully treated by needle revision[4,11]; this type of bleb was not present in our series. Our overall rate of 11 of 12 complete or qualified

successes was comparable to that reported by other authors. Our series included several complex patients with multiple previous operations, including failure after 5-fluorouracil trabeculectomy, in whom the prognosis for achieving a successful filter by any conventional technique was considered poor.

Bleb failure with subsequent intraocular pressure increase may occur in the early perioperative period or at any time thereafter. While a pressure increase in the first few weeks to months following surgery may signify a transient hypertensive phase[13] or response to topical corticosteroids, true bleb failure results in a permanent intraocular pressure increase and concomitant risk of continued optic nerve damage. Some authors have advocated needle revi-

sion solely in the perioperative phase,[3,5] while others have found the interval between surgery and needle revision to make little difference.[8] This interval was variable in our series and depended on the clinical circumstances. It did not seem to influence the results. Patients with an interval ranging from two weeks to ten years between original filtration surgery and needle revision responded successfully to needle revision.

Anatomically, the site of failure may be localized to the intraocular, intrascleral, or subconjunctival regions.[14] Most failures after glaucoma surgery involve scarring of the subconjunctival tissues. This appeared to be the situation in our series as the limbal stomas were patent by gonioscopy in all instances.

The positive experience with postoperative subconjunctival 5-fluorouracil in complicated filtering surgery[9] and in inflammatory glaucoma[2] has suggested a beneficial role in other difficult situations. Our more recent patients all received treatment with 5-fluorouracil; some had received 5-fluorouracil therapy with previous filtering surgery. Although we were not able to demonstrate a statistically significant benefit from the use of 5-fluorouracil, our clinical impression was that it was advantageous. The patients in whom it was used had significantly more previous surgery and hence would have been expected to have failure more frequently.

The complications of 5-fluorouracil, especially those involving the corneal surface, are well known.[15] We experienced a tolerable rate of complications, the most severe being corneal erosions, all of which healed without sequelae.

We have found transconjunctival needle revision to be a simple, safe, and efficacious method of restoring bleb function. The use of 5-fluorouracil as an adjunct to needle revision may be helpful, especially in situations where inflammation, multiple previous operations, or other high-risk features exist. Transconjunctival needle revision should be considered a useful option in the management of the failed or failing filtering bleb.

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The Effect of Iridotomy on Iris Contour

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With a recently developed technique for quantifying the geometry of the anterior chamber in optical cross section (slit-lamp photography using the Scheimpflug principle and computer correction for the optical effects of the cornea), we studied the iris contour before and after iridotomy in six patients with narrow anterior chamber angles and angle-closure glaucoma. Before iridotomy, the iris contour was convex anteriorly in all meridians. After iridotomy, the anterior lens surface position did not change perceptibly. The iris at the pupil margin settled backward onto the lens surface, no longer held forward by the narrow stream of aqueous passing from the posterior chamber to the anterior chamber. Next to the pupil there was often a perceptible mound, presumably representing the iris sphincter. From the point of support by the lens to the root of the iris, the contour of the iris surface was a straight line, except for the surface irregularities. The deepening of the anterior chamber at each point was the difference between the convex contour before iridotomy and the straight line after iridotomy.

CLINICAL ASSESSMENTS of the anterior chamber and the anterior chamber angle have been qualitative gonioscopic descriptions or semi-quantitative estimates.[1-5] Although the central anterior chamber depth can be measured by pachymetry, other regions of the anterior chamber are more difficult to quantify. Such measurements are possible from slit-lamp photography.[6] Optical cross sections in various meridians can be accomplished with a rotating slit-lamp camera that utilizes the Scheimpflug principle, and the true position of the iris and lens can be determined by computed correction of the image for the effects of the cornea.[7] This recently developed method should allow study of the anterior chamber anatomy, physiologic aspects of relative pupillary block, and pathophysiologic aspects of angle-closure glaucoma. There may be anatomic differences to explain why some narrow angles become closed but others do not, and it may be possible to distinguish between subvarieties of angle-closure glaucoma, such as relative pupillary block (primary angle closure), plateau iris, or glaucoma caused by forward lens movement (for example, ciliary block).

Subjects and Methods

After Institutional Review Board approval, patients were recruited for the study who were about to undergo laser iridotomies upon the recommendation of their attending physician. Patients who provided written informed consent had slit-lamp photographs taken of both eyes before and one to six months after laser iridotomy. In all patients a photograph was taken with the pupil in a natural position, and in most patients additional photographs were taken with pharmacologically constricted or dilated pupils, either before or after iridotomy, or both.

This initial study includes 12 eyes of six patients. Four eyes of three patients had narrow angles and the other eight eyes had chronic angle-closure glaucoma (three bilateral and two unilateral cases) characterized by increased intraocular pressure associated with apposition of the iris against the trabecular meshwork over part or all of the circumference, without synechiae formation.

To quantify the iris contour, photographs were taken with a rotating slit-lamp camera.

With this camera, the illuminating slit beam that formed an optical cross section of the anterior chamber was directed along the anteroposterior axis of the eye and photographed at a viewpoint angle of 45 degrees with the film plane tilted an additional 45 degrees to be perpendicular to the plane of slit illumination (Scheimpflug principle). The slit beam and camera could be rotated around the anteroposterior axis of the eye. Images were obtained in the horizontal, vertical, and two oblique meridians, with the result that images of the iris contour were obtained in eight meridians around the circumference of the eye. Computed calculations were used to correct for distortion caused by the tilted film plane and by the image displacement by the optics of the cornea. The details of the photographic and computational photographic methods were the same as published in detail previously,[7] except that to correct for the optical effects of the cornea, in this study we utilized a slightly different and simpler calculation method devised in collaboration with Stephen Russell, M.D. (St. Louis University, St. Louis, Mo.). We took the corneal curvature from the curvature in the photograph under analysis (rather than fitting a three-dimensional paraboloid surface from several photographs). Additionally, ray tracing was done with the use of Snell's law in a single plane rather than through three-dimensional vector algebra. The angles of incidence and refraction were determined by linear interpolation between two data points rather than fitting the series of data points to a curve expressed as a paraboloid. Finally, the anteroposterior axis used in the analysis was the photographic axis, the line parallel with the photographic frame that passes through the center of the Purkinje image. The camera is designed so that in an average normal eye the photographic axis should coincide with the optical axis of the eye.[8] (In the previously described method,[7] the coordinates of all points were transformed to use the visual axis for reference rather than the optical axis.) Central anterior chamber depth was also measured with an optical pachymeter and central corneal curvature determined with a keratometer.

The computer-corrected images were studied in two ways. For qualitative description, tracings of the surface contours before and after iridotomy were superimposed in all eight meridians of all 12 eyes. The anterior chamber depth (corneal epithelium to lens or iris surface) was determined from the X,Y coordinates

of these surfaces in the plane of the image at 1.0-mm intervals radially from the photographic axis.

Results

In these 12 eyes, the central anterior chamber depth (endothelium to lens surface) ranged from 1.6 to 1.9 mm. In no case did the measurement by optical pachymetry differ by more than 0.06 mm from the measurement along the photographic axis of the computer-corrected slit-lamp image. There was no statistically significant change in position of the anterior lens surface after iridotomy, but a suggestion that the lens surface is about 0.05 mm more posterior after iridotomy. Interestingly, this change is of the same magnitude and direction as that observed by Jacobs and Krohn,[9] and the change was also considered by them equivocal and, if real, both negligible and of uncertain cause.

The major effect of iridotomy is on the iris position, evident at distances of 2, 3, and 4 mm from the photographic axis. The anterior chamber depth (endothelium to lens/iris surface) increased measurably in all meridians, and the change was statistically significant (Student t-test, $P < .05$ in all cases). In most eyes there was no measurable space before iridotomy between the cornea and iris 5 mm from the photographic axis, whereas there was a measurable anterior chamber depth at this location after iridotomy (Table). We observed a greater change in iris position than did Lee, Brubaker, and Ilstrup,[6] who made depth measurements along the inferior meridian only. The likely explanation is that the anterior chamber depth in our patients was on the average less than in theirs, and presumably therefore our patients had a larger bombé effect.

Before iridotomy the anterior iris surface had a smooth curved contour if minor surface irregularities were ignored. The curvature is relatively flat toward the pupil, but has a decreasing radius of curvature toward the periphery. The shape of the curve is not described by a simple mathematical expression, but is quantitatively predictable from pupil diameter, anteroposterior pupil position in relation to the iris root, and the existence of a pressure difference between the posterior and anterior chambers (James Tiedeman, M.D., written and oral communications, April 1981 to May 1990).

After iridotomy, the iris contour changes (Fig.

TABLE
DEPTH OF ANTERIOR CHAMBER (MM ± S.D.) BEFORE AND AFTER IRIDOTOMY

MERIDIAN	LASER IRIDOTOMY	RADIAL DISTANCE (MM) FROM CENTRAL PHOTOGRAPHIC AXIS											
		0		1		2		3		4		5	
		NO.	DEPTH	NO.	DEPTH	NO.	DEPTH	NO.	DEPTH	NO.	DEPTH	NO.	DEPTH
Temporal	Before	11	1.62±0.12	8	1.59±0.12	11	1.09±0.11	11	0.86±0.13	11	0.52±0.15	5	0.26±0.09
	After	11	1.69±0.13	8	1.64±0.14	11	1.31±0.16	11	1.15±0.12	11	0.90±0.15	11	0.39±0.19
Supero-	Before	10	1.64±0.10	10	1.47±0.23	11	1.07±0.25	11	0.75±0.20	11	0.44±0.20	5	0.15±0.08
temporal	After	10	1.70±0.12	10	1.68±0.16	11	1.32±0.12	11	1.10±0.15	11	0.83±0.16	10	0.40±0.18
Superior	Before	9	1.62±0.12	10	1.53±0.17	10	1.06±0.16	11	0.73±0.13	11	0.40±0.13	4	0.16±0.10
	After	9	1.65±0.13	10	1.65±0.21	10	1.27±0.23	11	0.97±0.16 ·	11	0.81±0.18	9	0.41±0.18
Supero-	Before	11	1.63±0.16	10	1.47±0.27	11	1.05±0.18	11	0.76±0.13	11	0.44±0.21	6	0.22±0.07
nasal	After	11	1.66±0.11	10	1.47±0.20	11	1.19±0.11	11	0.99±0.13	11	0.70±0.18	7	0.35±0.20
Nasal	Before	10	1.64±0.12	10	1.48±0.23	10	1.00±0.14	10	0.73±0.16	10	0.40±0.11		—
	After	10	1.70±0.12	10	1.55±0.24	10	1.16±0.15	10	0.98±0.15	10	0.66±0.16	6	0.27±0.20
Infero-	Before	9	1.65±0.14	10	1.38±0.27	11	0.90±0.18	11	0.65±0.17	11	0.33±0.11		—
nasal	After	9	1.66±0.14	10	1.46±0.19	11	1.04±0.14	11	0.90±0.11	11	0.56±0.15	6	0.17±0.08
Inferior	Before	10	1.64±0.13	10	1.29±0.27	11	0.91±0.17	10	0.61±0.14	11	0.30±0.10		—
	After	10	1.71±0.15	10	1.40±0.24	11	1.17±0.21	10	0.97±0.12	11	0.60±0.18	6	0.30±0.23
Infero-	Before	10	1.63±0.14	9	1.48±0.25	11	0.97±0.20	11	0.65±0.16	11	0.36±0.16		—
temporal	After	10	1.69±0.14	9	1.59±0.26	11	1.14±0.25	11	0.91±0.18	11	0.65±0.20	7	0.27±0.07

1). The iris next to the pupil drops posteriorly by a slight amount, demonstrating that it had been held forward slightly by the thin stream of aqueous passing from the posterior chamber into the anterior chamber. The iris near the pupil has a slight concave curvature corre-
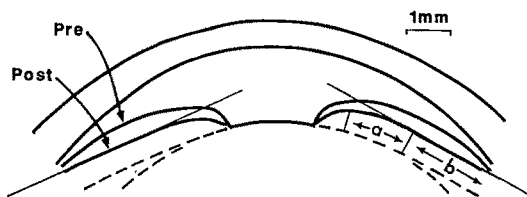
Fig. 1 (Jin and Anderson). Computer-corrected optical cross section of the anterior segment with superimposition of the contours of the anterior iris surface before and after iridotomy. Actual positions of visible surfaces are in solid lines (the lens surface obtained from a separate photograph taken with a dilated pupil). The presumed position of the posterior iris surface after iridotomy and of the peripheral extension of the anterior lens surface are in dashed lines. In the region marked "a," the iris contour after iridotomy conforms to the lens surface on which it is draped. The region marked "b," the mid-section and peripheral iris after iridotomy, has a straight contour, as indicated by the thin straight line.

sponding to the curvature of the anterior lens surface upon which it rests. (The position of the anterior lens surface was determined by superimposing photographs of the same eye in the same meridian taken with a dilated pupil.) In some instances (Fig. 2), there was a detectable additional mound, presumably related to additional iris thickness in the region of the iris sphincter muscle. Such a mound was never evident in eyes without iridotomy.

The mid-peripheral and peripheral iris conforms to a straight line from the edge of its support by the lens to its point of attachment at the root of the iris.
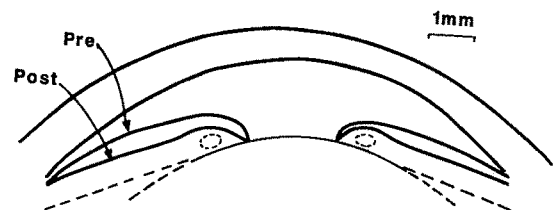
Fig. 2 (Jin and Anderson). Similar image as in Figure 1, showing the juxtapupillary mound in the iris contour. This mound is presumably caused by the iris sphincter, the assumed position of which is indicated with a dashed line.

Discussion

The effect of iridotomy is to relieve relative pupillary block, making the pressures in the posterior chamber and anterior chamber equal. The iris contour is no longer determined by a pressure difference between the posterior chamber and anterior chamber. The change in contour after iridotomy has several features. The pupillary margin drops backward, no longer supported by the posterior chamber pressure and the stream of aqueous passing through the pupil, but supported now by the lens surface. Therefore in the peripupillary region the contour of the anterior iris surface conforms to that of the lens upon which it is draped, except for variations in iris thickness, such as that caused by the presence of the sphincter muscle near the pupillary margin. More peripherally, the flat configuration of the iris conforms to expectations for tissue slightly under stretch, extending in a straight line from its root attachment to the edge of its support by the anterior lens surface. There is no billowing of the iris, because there is no longer a difference of pressure between the anterior and posterior chambers. Our measurements did not detect what must be a small effect of gravity resulting from the difference in specific gravities of iris and aqueous humor.

The anterior chamber deepening at any point is the difference in position of the preiridotomy contour and the postiridotomy contour. Of particular interest is the deepening in the region of the trabecular meshwork. In the patients described here the angle widened in a typical manner as the steeply curved peripheral iris became flat. It might be speculated that when the angle fails to deepen after iridotomy there was a gentler curvature to the peripheral iris, or that the effective position of the iris root attachment in relation to the meshwork was altered by peripheral synechiae or abnormal ciliary body configuration.

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Use of the Megasoft Bandage Lens for Treatment of Complications After Trabeculectomy

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Shallow anterior chambers and leaking filtration blebs are possible complications after trabeculectomy that can be treated with therapeutic contact lenses. In most cases, however, treatment fails because these lenses are not large enough to cover the filtering bleb. We evaluated the use of a newly developed large diameter (20.5 mm) therapeutic soft contact lens. Five patients with shallow anterior chambers and ten patients with leaking filtering blebs after trabeculectomy were fitted with this new extended-wear contact lens. All patients with shallow anterior chambers developed deep chambers after a mean treatment period of five days. Of the ten patients with leaking filtering blebs, in eight (80%) the leak closed after a mean treatment period of 2.2 months. The contact lens used was comfortable and complications occurred in only one eye. This new therapeutic device is an improvement in the treatment of complications after trabeculectomy.

TRABECULECTOMY is the most frequently used surgical technique to treat glaucoma. The purpose of this procedure is drainage of aqueous humor beneath the conjunctiva by connecting the anterior segment of the eye with the subconjunctival space. A successful trabeculectomy is generally characterized by formation of a filtering bleb, which is a subconjunctival accumulation of aqueous. Complications after trabeculectomy include a shallow or flat anterior chamber or the leakage of the filtering bleb.

The prevalence of a shallow anterior segment after a routine trabeculectomy is 5% to 13%, whereas the prevalence of a flat anterior chamber is 3% to 4%.[1] A shallow or flat anterior chamber may be associated with choroidal detachment, malignant ciliary block glaucoma, peripheral anterior synechiae formation, cataract formation after a lens-cornea touch, corneal decompensation, or bleb failure.[2,3] In most cases a shallow or flat anterior chamber is brought on by excessive filtration. To avoid immediate collapse of the anterior chamber a viscous substance such as sodium hyaluronate can be injected into the anterior chamber.[4,5]

A complicated excessive filtration can sometimes be inhibited with the use of a Simmons tamponade shell. This is a scleral contact lens with a raised platform on its inner surface. The shell is placed on the eye with the platform pressing against the leaking region, supplemented by a pressure patch dressing.[6] A complication associated with this kind of treatment is rotation of the shell with pressure applied at the wrong region, which causes flattening of the anterior chamber and bleb failure.[7,8]

Leakage of filtering blebs in the immediate early postoperative period is usually caused by poor wound healing or opening of sutures. The bleb leaks seen as a late complication are usually brought on by excessive thinning.[7] The most serious consequence of a leakage of the filtering bleb is intraocular infection.[9] When the leak is substantial a shallow or flat anterior chamber and hypotony can develop.

Management of a filtering bleb leak may include resuturing, pressure patching, application of cyanoacrylate glue, soft therapeutic contact lenses or a Simmons tamponade shell, conjunctival resection, or conservative therapy with antibiotics, carbonic-anhydrase inhibitors, and beta blockers.[10-12] The use of soft therapeutic contact lenses to seal bleb leaks has been reported.[9,10] In most cases treatment fails, however, because the diameter (maximum 15.0 mm)

of the lenses used was not large enough to cover a filtering bleb.

To overcome this problem we evaluated the use of a large diameter (20.5 mm) soft therapeutic contact lens in the management of shallow or flat anterior chambers and leaking filtration blebs. This Megasoft Bandage Lens was assessed in 15 patients and is considered an important new device in the treatment of complications after trabeculectomy.

Patients and Methods

Fifteen consecutive patients with postoperative complications after trabeculectomy were fitted with the Megasoft Bandage Lens. Five eyes had developed a shallow or flat anterior chamber without leakage and ten eyes had a leaking filtration bleb. Of the 15 patients, ten were women and five were men. They ranged in age from 40 to 77 years (mean, 65.3 years). The diagnosis before surgery was primary open-angle glaucoma in nine eyes, chronic angle-closure glaucoma in three eyes, low-tension glaucoma in one eye, and secondary open-angle glaucoma in two eyes.

The Megasoft Bandage Lens consists of xylofilcon B material, which has a water content of 76.5% and an oxygen permeability of 46 Dk, and is composed of a terpolymer of vinyl pyrrolidone with specially patented hydrophobic monomers that offer high tensile strength. The lens is bicurved with a base curve of 10.0 mm and a scleral curve of 12.5 mm. The central thickness is 0.38 mm and the diameter is 20.5 mm. The optical power of the lens is 0 diopters.

During treatment the Megasoft Bandage Lens was worn continuously (day and night) and was removed only during the checkups at the contact lens department. The lens was replaced after a maximum wearing period of three months. Patients were examined regularly for corneal decompensation, corneal microcysts, stromal striae, Descemet's folds, neovascularization, ocular infection, and the acute red eye syndrome, complications that may specifically be induced by extended contact lens wear. Anterior chamber depth and intraocular pressure were also examined regularly. Wound leaks and bleb leaks were checked with the Seidel fluorescein test. All patients received a prophylactic medication consisting of gentamicin sulfate 0.5% eyedrops and Vidisic gel three times daily.

Results

The Megasoft Bandage Lens was used in five patients in whom the anterior chamber did not reform spontaneously within a few days after trabeculectomy. The Seidel fluorescein test was negative, which indicated that no leakage occurred. In this group lenses were applied between one and ten days after trabeculectomy (Table 1). The mean treatment period was five days (range, two to nine days). All eyes responded favorably to the treatment. The mean time to develop a normal anterior chamber was 2.4 days (range, one to six days). In one case removal of the lens was followed by an entire anterior chamber collapse within a few hours. This induced a lens-cornea touch and cataract formation (Case 5).

In the patient group with leaking filtration

TABLE 1

TREATMENT OF COMPLICATIONS AFTER TRABECULECTOMY WITH THE MEGASOFT BANDAGE LENS IN PATIENTS WITH A SHALLOW OR FLAT CHAMBER

CASE NO.	DIAGNOSIS	INTERVAL TRABECULECTOMY AND LENS PLACEMENT (DAYS)	ANTERIOR CHAMBER REFORMATION (DAYS)	TREATMENT PERIOD (DAYS)	ABNORMALITY INDUCED BY LENS	COMPLAINTS	RESULTS
1	Primary open-angle glaucoma	4	6	9	None	None	Positive
2	Primary open-angle glaucoma	7	1	5	None	None	Positive
3	Secondary open-angle glaucoma	7	2	5	None	None	Positive
4	Chronic angle-closure glaucoma	10	2	2	None	None	Positive
5	Chronic angle-closure glaucoma	1	1	3	None	None	Negative

TABLE 2
TREATMENT OF COMPLICATIONS AFTER TRABECULECTOMY WITH THE MEGASOFT BANDAGE LENS
IN PATIENTS WITH A LEAKING FILTRATION BLEB

CASE NO.	DIAGNOSIS	INTERVAL TRABECULECTOMY AND LENS PLACEMENT	TREATMENT PERIOD	ABNORMALITY INDUCED BY LENS	COMPLAINTS	RESULTS
1	Primary open-angle glaucoma	1 day	2 wks	Present	Present	Positive
2	Primary open-angle glaucoma	1 day	3 wks	None	None	Positive
3	Chronic angle-closure glaucoma	4 days	2 wks	None	None	Positive
4	Primary open-angle glaucoma	5 days	1 mo	None	None	Positive
5	Primary open-angle glaucoma	9 days	10 days	None	None	Positive
6	Primary open-angle glaucoma	2 wks	10 wks	None	None	Positive and negative
7	Primary open-angle glaucoma	3 wks	5 wks	None	None	Positive
8	Primary open-angle glaucoma	2 mos	7 mos	None	None	Positive
9	Low-tension glaucoma	3 mos	5 mos	None	None	Positive
10	Secondary open-angle glaucoma	6 mos	3 mos	None	None	Positive and negative

blebs, the Megasoft Bandage Lens was applied at various intervals after trabeculectomy (Table 2). The mean time between the operation and application was 5.2 weeks (range, one day to six months). The patients who were treated shortly (within ten days) after the trabeculectomy had wound leaks (Case 1 through 5), whereas the patients treated long (within six months) after the trabeculectomy had large cystic diffuse leaking blebs (Cases 6 through 10). The mean wearing time was 2.2 months (range, ten days to seven months). The Seidel fluorescein test was used to determine whether the leakage had stopped or not. Of ten eyes, in eight (80%) the Seidel test became negative after treatment (Table 2). In two cases (Cases 1 and 5) the bleb leaks were first resutured and glued without any success. After applying a Megasoft Bandage Lens the leak was sealed within 1.5 and two weeks, respectively. In one patient (Case 8), there was still a diffuse leakage after seven months of treatment with the Megasoft Bandage Lens. The bleb was resutured and glued without success. A Megasoft Bandage Lens was reapplied and one week later the leak had closed. Two eyes (Cases 6 and 10) still had a slight diffuse leakage after 2.5 and three months, respectively, of treatment. Because the leakage was minimal the Megasoft Bandage Lens was removed and no further treatment was believed to be necessary. The Megasoft Bandage Lens induced no corneal complica-

tions, except in one patient with lens binding in a dry eye (Case 1, Table 2).

Discussion

The use of a Megasoft Bandage Lens is an improvement in the treatment of complications after trabeculectomy in patients with glaucoma. In patients with a shallow or a flat anterior chamber, treatment with the Megasoft Bandage Lens stimulates the reformation of the anterior chamber. All patients in this group developed a deep anterior chamber within a few days after treatment with the Megasoft Bandage Lens. A possible explanation for these findings is that the Megasoft Bandage Lens stops the transconjunctival filtration and therefore promotes a reformation of the anterior chamber. A direct pressure effect seems to be unlikely. Eventually during the process of wound healing an equilibrium will develop and the lens can be removed. In one eye the chamber collapsed a few hours after removing the lens. This observation shows that the equilibrium is not always a stable one and that the chamber depth should be examined frequently after removal of the lens.

We do not know in how many eyes of this group the anterior chamber would have reformed spontaneously without treatment. We

do know that complications induced by a flat anterior chamber can be severe. The use of the Megasoft Bandage Lens is a simple method without side effects, unlike other interventions to deepen the anterior chamber, such as pressure patching, which is often associated with bleb failure.[2] Use of the Megasoft Bandage Lens has not been associated with bleb failure.

The results in the patient group with the leaking filtering blebs suggest that the Megasoft Bandage Lens promotes the closure of a filtration bleb leak. We believe that the Megasoft Bandage Lens, by slowing down or even stopping the leak flow, allows a restoration of the epithelial barrier function and consequently the closure of the bleb leak. This group includes patients with wound leaks developed shortly after surgery and patients with large cystic diffuse leaking blebs, which developed as a late surgical complication. The epithelial healing of the large cystic diffuse leaking blebs especially needs time. This is reflected in the vast difference of the mean period of treatment between the group with a shallow or flat anterior chamber (five days) and the group with a leaking bleb (2.2 months). Suture repair and glue application often fail in the cystic paper-thin blebs. Treatment with the Megasoft Bandage Lens is an effective alternative in these cases.

Fourman and Wiley[13] reported the use of a collagen shield (diameter, 14.5 mm) to treat a leaking filtration bleb. Such a collagen shield dissolves slowly, and the period of dissolution can span from approximately six hours up to 72 hours.[14] We believe the short duration of action and the relatively small size of these collagen shields make them less suitable for the treatment of oversized diffuse leaking blebs.

Despite the large size of the Megasoft Bandage Lens the results show that it can be used continuously for long periods without any complications. Problems associated with therapeutic soft contact lens wear, such as corneal edema, ocular infection, sterile hypopyon, and corneal infiltrates, did not occur.[15,16] One patient developed an epithelial detachment when the lens was removed. This was probably caused by contact lens fixation in a dry eye. All other patients used the Megasoft Bandage Lens without any problems or complaints and noted the lens to be comfortable. Two patients used the Megasoft Bandage Lens for five and seven months continuously without any complications. This is probably because of the high water content (76.5%) of the Megasoft Bandage

Lens, which allows for good corneal oxygenation.[17]

Compared with the conventional soft therapeutic contact lens the most important advantage of the Megasoft Bandage Lens is the diameter (20.5 mm). Because of this it can even be applied on eyes with large cystic blebs without any difficulties. In most cases of large blebs the conventional soft therapeutic contact lens does not fit properly.

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OPHTHALMIC MINIATURE

My grandfather was a head taller than my grandmother but looked more, because he was very thin. His face had the well-lined skin of a man who has spent his whole life outdoors. He had a thin salt-and-pepper moustache, interrupted by a generous nose. His back was slightly rounded, so that his head perched above the ground more than atop his body. And as for his eyes: one eye always squinted, and his head was always turned so that that eye was closer to you. Bowed forward, one eye squinting, he looked like a jeweler studying the bounce of light within you.

Richard Zabel, *The Swan, The Atlantic*, May 1990, p. 101

Oxygen Permeability of Disposable Soft Contact Lenses

Barry A. Weissman, O.D., Steven D. Schwartz, M.D.,
Nina Gottschalk-Katsev, B.A., and David A. Lee, M.D.

Disposable contact lenses are inexpensive hydrogel lenses that are approved for both daily and extended wear. Confusion may exist regarding the physical properties of disposable contact lenses. We used the single-chamber polarographic oxygen permeability measurement method, corrected for both boundary and edge effects, to determine objectively the oxygen permeability of three brands of disposable contact lenses. The oxygen permeability values determined for each lens material are as follows: Acuvue, 18×10^{-11} cm^2 ml O_2/sec ml mm Hg (Dk); NewVues, 15×10^{-11} Dk; and SeeQuence, 9×10^{-11} Dk. This demonstrates that the inexpensive production techniques, which confer a relatively low unit expense, do not change the physical properties of the hydrogel materials as they relate to oxygen permeability and transmissibility. We concluded that hypoxic stress to the cornea is just as likely when using a disposable contact lens as it is when using a conventional reusable soft hydrogel lens of similar composition and water content.

RECOMMENDATIONS REGARDING the ideal length of wear for contact lenses have changed dramatically over the last decade. Appropriately, manufacturers now defer the decision whether to prescribe contact lenses on a daily- or extended-wear basis to the contact lens provider. Despite clear and informative literature made available by manufacturers, confusion exists regarding the physical properties that make

disposable contact lenses disposable. Subsequently, improper assumptions regarding the physical properties of disposable compared with traditional hydrogel contact lenses may result. Specifically, we address the question of whether disposable lenses differ in oxygen permeability from the reusable lenses made from similar materials provided over the last decade.

Oxygen permeability, the intrinsic ability of a material to transmit oxygen by diffusion, has become one of the most important features of modern contact lens material. Oxygen transmissibility is the ability of a specific contact lens of a given thickness to transmit oxygen by diffusion. The single-chamber polarographic oxygen transmissibility and permeability measurement method has served as the industry standard for many years, although it has been challenged by several published reports.[1-5] Two specific difficulties have been identified with the use of the single-chamber polarographic method for lenses of high oxygen transmissibility values: the boundary and edge effects. The boundary effect originates from consideration of potential fluid layers on one or both surfaces of the sample being studied.[6,7] This results in underestimation of both oxygen permeability and oxygen transmissibility. The edge effect, conversely, considers the ability of the single-chamber polarographic cathode to collect diffusing oxygen from an area in the sample somewhat greater than its own diameter. This results in overestimation of both oxygen permeability and oxygen transmissibility.[8,9]

Correction techniques have been devised for both boundary and edge effects.[7,8,10] Although the coulometric carrier gas method has become accepted as the method of choice for rigid gas-permeable lenses and materials, the single-chamber polarographic method, corrected for boundary and edge effects, remains the standard for use with hydrogel materials.[11]

Correction for the edge effect is a simple calculation applicable to all hydrogel lenses, but correction for potential boundary effects involves multiple single-chamber polarographic measurements of the oxygen transmissibility

of the same sample material at different thickness values.[7] Manufacturers have been able to provide samples of different thicknesses in the past, with lathing being a primary method of contact lens production. The increasing popularity of more cost-effective molding production techniques, however, has led to a class of lenses available only in certain set designs and, more specifically, fixed thicknesses. Examples of such limited-design devices would be collagen shields and disposable hydrogel lenses. Weissman and Fatt[12] and Weissman and associates[13] have shown that it is possible to stack samples of hydrogel materials to provide samples of multiple thicknesses for use in oxygen permeability measurement by the single-chamber polarographic method and have applied this method to study oxygen permeability and transmissibility of collagen shields. In this study, we measured oxygen permeability values for several examples of disposable contact lens materials.

Material and Methods

Ten sample disposable hydrogel contact lenses were obtained from each of three manufacturers. These lenses were Acuvue (Johnson and Johnson, nominally 42% etafilcon and 58% water) −0.75 diopter; NewVues (Ciba Vision, nominally 45% vifilcon A and 55% water) −0.75 diopter; and SeeQuence (Bausch & Lomb, nominally 61.4% poly [2-hydroxyethylmethacrylate] and 38.6% water) −1.00 diopter. Low minus powers were specifically chosen so we would be able to measure essentially parallel-sided shells of material.[14] Twelve 10-ml plastic containers were used, and one lens, two lenses, three lenses, and four lenses of each type were placed into these containers in groups. The containers were then filled with 5 ml of fresh 0.9% unpreserved saline.

The single-chamber polarographic method described by Fatt[1] and Fatt and Chaston[7] was used to measure the oxygen permeability values of the three disposable contact lens materials, with the same assumptions and precautions. A polarographic oxygen sensor, which consists of a 4-mm diameter gold cathode and surrounding silver-silver chloride ring anode, was mounted in a plastic holder. This was connected to a Schema Versatae 920A amplifier (Berkeley, California), which was precalibrated with three known resistors. The voltage

between the anode and cathode was maintained at a constant 0.7 V, and the resultant current was amplified. A linear strip chart recorder graphed the changes in current and was used to determine when current became constant so that the oxygen transmissibility of samples could be determined.

Since oxygen transmissibility is temperature dependent, the apparatus was maintained at 35 C to simulate ocular temperature by using a surrounding foam box and a thermostat-controlled 60-W light bulb. Paper towels saturated in hospital-grade sterile irrigation water were placed on the floor of the box to maintain high humidity so that samples would not dehydrate during the course of the experiment. Five hours were allowed for temperature and humidity equilibration within the box before measurement of the samples. The sample lenses, in groups within separate containers, and a fresh bottle of unpreserved 0.9% saline were kept within the box during this time to facilitate their thermal equilibration.

Before measurements were taken, the single-chamber polarographic device was recalibrated with two known resistors, and the dark current was measured. An oxygen-impermeable plate of glass was placed over a saline-saturated cigarette paper on the sensor and a small zero oxygen or dark current was recorded at 2.5×10^{-7} A. This was subtracted from subsequent current measurements.

For the lens measurements, the lenses were removed from the containers and placed concave side down onto the tip of a plastic tube covered with a nylon mesh. Lenses were measured in stacks of one, two, three, and four samples. Each group was measured twice, with at least ten minutes separating each trial while the lenses, again in the containers, went through thermal and hydraulic re-equilibration. Care was taken to remove any air bubbles trapped between the samples before measurement. A drop of the preheated 0.9% saline was placed on the electrode surface, and then the plastic tube with the sample was inverted and inserted into the holder so that the samples were held flat on the electrode. Any residual fluid on the upper surface was removed with a cotton-tip applicator before measurement.

It took between two and five minutes for the polarographic current to reach an asymptote with the samples in place. This steady-state current, minus the previously determined zero oxygen current, was then used to calculate the oxygen transmissibility value for each stack of

samples. Two measurements were made at each thickness.

After an additional five to ten minutes of thermal and hydraulic re-equilibration, a pre-calibrated electronic thickness gauge was used to measure the central thickness of the lenses stacked in groups.[15] Care was taken not to compress the stacked lenses. As a control, after measurement of the samples in stacks, the lenses were separated and individual central-thickness measurements were made. Central-thickness measurements were not made for the SeeQuence lenses because they could not be separated from each other.

Finally, a hand refractometer was used to confirm the water content of each group of samples.[16] The lenses were spread out in groups on the measuring prism for the Acuvue and the NewVues, whereas the SeeQuence lenses were measured in a stack, because it was impossible to separate them.

The reciprocal of oxygen transmissibility for each group was multiplied by 1 = (4.72 × thickness) to correct for the edge effect.[8] This value was then plotted vs thickness, and the reciprocal of the slope of the linear regression of these data was obtained. This is the oxygen permeability of the material at 35 C, corrected for both edge and boundary effects.

Results

It was not possible to determine the water content for the NewVues by use of the hand refractometer, but water content for the other lenses was consistent with published nominal values (Table).

The sum of the central thicknesses of individual lenses was within 0.001 cm of the value found for stacked groups of lenses in all cases. It was not possible to separate the individual SeeQuence lenses once they had been firmly stacked and all air bubbles removed; however, the thickness values measured for groups of SeeQuence lenses were consistent with sums of individual thickness, which was 0.006 cm for the single sample.

The Figure shows the reciprocal of oxygen

TABLE
LENS MEASUREMENTS

LENS TYPE	WATER (%)	THICKNESS OF STACKED LENSES (CM)	OXYGEN TRANSMISSIBILITY $\left(\times 10^{-9} \frac{cm^2\ ml\ O_2}{sec\ ml\ mm\ Hg} \right)$ TEST 1	TEST 2	OXYGEN PERMEABILITY $\left(\times 10^{-11} \frac{cm^2\ ml\ O_2}{sec\ ml\ mm\ Hg} \right)$
Acuvue					
No. of stacked lenses					
One	60	0.012	15.02	15.67	18
Two	59	0.023	9.43	9.10	
Three	59	0.032	6.48	5.82	
Four	57	0.043	5.16	4.83	
NewVues					
No. of stacked lenses					
One	NP*	0.010	14.20	13.05	15
Two	NP	0.019	8.78	9.43	
Three	NP	0.026	5.82	5.82	
Four	NP	0.035	4.83	4.83	
SeeQuence					
No. of stacked lenses					
One	40	0.006	11.40	11.73	9
Two	39	0.012	6.15	7.13	
Three	39	0.017	4.51	4.18	
Four	40	0.024	3.85	4.01	

*NP indicates not performed, because it was not possible to measure the water content of the NewVues by hand refractometer.
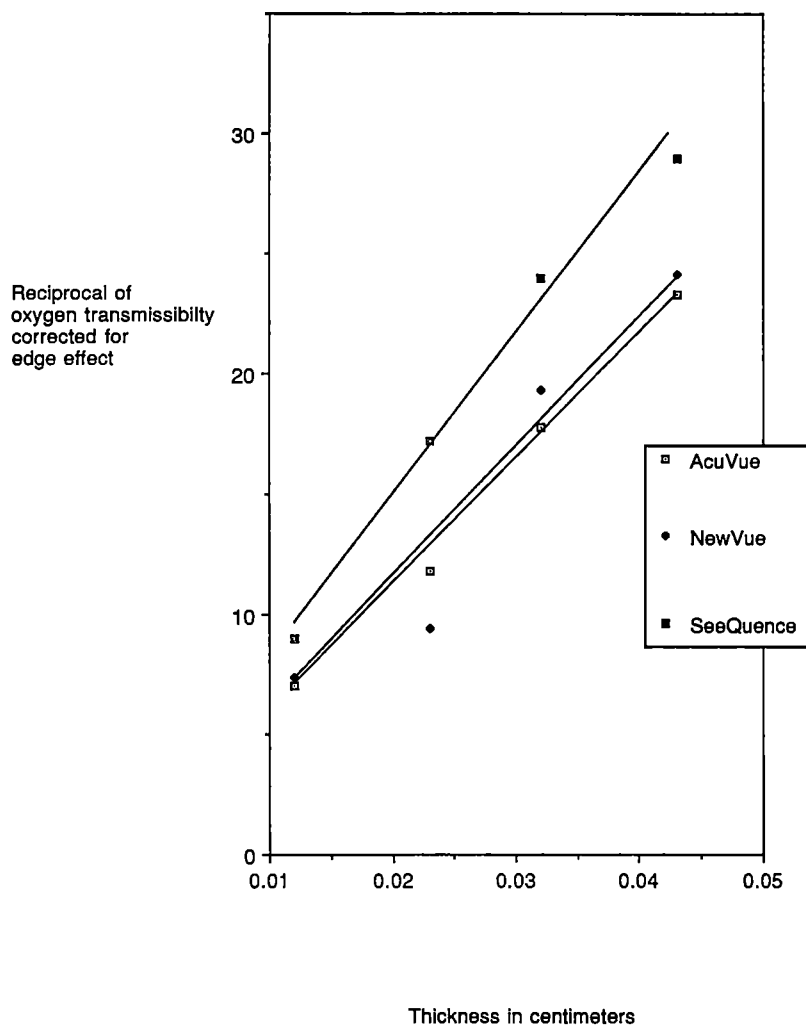
Figure (Weissman and associates). The reciprocal of oxygen transmissibility corrected for the edge effect is plotted vs thickness for the three groups of stacked lenses. The linear regressions for these data are shown. Data points shown represent two measurements for each thickness. The linear regressions and respective correlation coefficients are as follows: Acuvue, $y = (3.19 \times 10^5) = (5.62 \times 10^9)x$ [r = .99]; NewVues, $y = (4.89 \times 10^5) = (6.83 \times 10^9)x$ [r = .99]; SeeQuence, $y = (29.7 = 10^5) = (1.12 \times 10^{10})x$ [r = .97].

Thickness in centimeters

transmissibility corrected for the edge effect plotted vs thickness for the three stacked groups of lenses and the linear regressions for these data. The linear regression data and correlation coefficients (r) for each regression are better than $r = .95$ in all cases. The oxygen permeability values determined for each lens material are as follows: Acuvue, 18×10^{-11} cm^2 ml O_2/sec ml mm Hg (Dk); NewVues, 15×10^{-11} Dk; and SeeQuence, 9×10^{-11} Dk.

Discussion

Disposable contact lenses are hydrogel plastics molded inexpensively into designs similar to those previously accepted for extended wear. We evaluated whether the change in production

techniques for these lenses affects the oxygen permeabilities of these materials, because a change in oxygen permeability would change the potential for hypoxic stress to the cornea. This study provides objective, experimentally measured oxygen transmissibility values for disposable contact lenses.

Physical laws indicate that the oxygen transmissibility of a hydrogel lens is dependent upon the water content of the hydrogel, the thickness of the lens, and the temperature at which the measurement is made. Fatt and Chaston[7] have suggested that oxygen permeability may be estimated simply from the water content alone when temperature is stipulated.

The oxygen permeability values we determined are consistent with these physical relationships. This suggests that new inexpensive production techniques do not change the oxy-

gen permeability of hydrogel materials. The oxygen permeabilities of the disposable hydrogel contact lenses are virtually the same as those predicted and observed in reusable hydrogel contact lenses of similar water content and thickness.

It is therefore not surprising that some of the same clinical complications developing from extended-wear use of disposable contact lenses have been associated with extended wear of reusable hydrogel contact lenses.[17] A dramatic example of these possible complications are corneal ulcers associated with disposable contact lens wear.[18] These complications have been attributed, at least partially, to the sequelae of corneal hypoxia. Thus, the 'potential clinical advantage of these lenses does not develop from their oxygen transmissibility values, which are similar to those of other previously available hydrogel lenses. Potential advantages may, however, include their relatively decreased unit expense, so that disposability may allow for frequent, planned replacement. This frequent replacement may achieve a reduction of contact lens soilage and contamination associated with noncompliant lens wear and care. Furthermore, changes associated with the aging contact lens, such as cracks, may be reduced. Some studies do suggest potential optical and physiologic advantages when hydrogel lenses are used only for short periods of time and then replaced. Yet, despite the potential advantages, we predict from our results that disposable lenses are just as likely to cause hypoxic stress to the cornea as are other reusable hydrogel contact lenses of similar composition and water content.

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Treatment of Ocular Disease in Eczema Herpeticum

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Individuals with atopic dermatitis are particularly susceptible to herpes simplex viral infection and may develop dissemination (eczema herpeticum). Additionally, they may develop severe and bilateral herpetic ocular disease. The keratitis is commonly complicated by stromal scarring and slow epithelial healing despite topical antiviral therapy. We treated three patients who had herpetic keratoconjunctivitis associated with eczema herpeticum. In all three cases the keratitis resolved promptly (48 to 72 hours) without residual scarring after treatment with systemic acyclovir and topical trifluridine. The combined use of systemic acyclovir and topical trifluridine may be of similar value in treating all cases of atopic herpetic keratitis.

Atopic dermatitis affects about 1% of the general population of the United States. Patients have a low threshold for pruritus and develop characteristic skin changes of eczema in response to rubbing or scratching. Although atopic dermatitis typically begins in early infancy, individuals with this disease frequently develop other atopic manifestations later in life such as hay fever, allergic rhinitis, and asthma.[1] Other characteristics include immediate IgE mediated skin test reactions, increased serum IgE level, and defects in cell-mediated immunity.[1-3]

Individuals with atopic disease are particularly susceptible to herpes simplex infections, presumably because of depressed T lymphocyte function, and may develop a widespread herpetic infection referred to as Kaposi's varicelliform eruption or eczema herpeticum.[1,4-6] Eczema herpeticum is most common in childhood, which parallels the prevalence of atopic dermatitis, but severity appears to be unrelated to the extent of eczematous lesions present at the time of infection.[6] Vesicular skin lesions may be accompanied by fever and secondary bacterial skin infections,[7,8] and in severe cases viral infection of the lungs, brain, and adrenal glands can occur. Because of the potential severity of eczema herpeticum, systemic acyclovir is recommended for treatment.[9-11]

Ocular findings associated with atopic dermatitis include blepharitis, hay fever conjunctivitis, atopic keratoconjunctivitis, cataracts, and keratoconus.[12,13] Individuals with atopic disease are also particularly susceptible to ocular herpetic disease. Easty and associates,[13] Garrity and Liesegang,[12] and Wilhelmus, Falcon, and Jones[14] have reported that herpes keratitis in patients with atopic disease is commonly bilateral, and often accompanied by stromal scarring and slow epithelial healing despite antiviral therapy. We have similarly noted unusually severe keratitis and poor therapeutic response to topical antivirals in these patients.

We treated three patients who had herpetic keratoconjunctivitis associated with eczema herpeticum with systemic acyclovir and topical trifluridine. In all three patients the keratitis resolved promptly with no residual scarring. The use of systemic acyclovir and topical trifluridine may be of similar value in treating all cases of atopic herpetic keratitis.

Case Reports

All three patients were referred to our institution and were treated as inpatients between May 1988 and March 1989. We based the diagnosis of eczema herpeticum on the atopic histo-

ry, the disseminated nature of the vesicular skin lesions, and positive results of laboratory studies for herpes simplex.

Case 1

An 18-year-old woman with atopic dermatitis since infancy had a seven-day history of pain in the left eye. She had noted fever and malaise for seven days and a diffuse painful rash for three days. The patient had had recurrent labial cold sores, but none in the previous three months. She denied previous ocular herpetic disease. On examination she was found to be extremely uncomfortable and had a diffuse erythematous, vesicular rash over her face, neck, back, and chest (Fig. 1). Crusting and swelling were present in the area of the rash. The patient had tender preauricular lymphadenopathy. The eyelids were swollen and both new and crusted vesicles were noted bilaterally. A marked papillary conjunctival reaction was observed in the left eye, as were multiple corneal dendrites and a geographic lesion (Fig. 2). Corneal sensation of the left eye was diminished. The right cornea was normal. A Tzanck smear of the skin lesions showed multinucleated giant cells, and the results of both skin and conjunctival cultures were positive for herpes simplex virus type 1.

The patient was hospitalized and treated with intravenous acyclovir, 5 mg/kg of body weight every eight hours. Additionally, topical trifluridine was administered in the left eye every three hours. Twenty-four hours after instituting therapy the dendrites had disappeared, and there was only a small epithelial defect in the region of the geographic ulcer. Within 48 hours, the epithelium was healed completely and only faint ghost dendrites remained. The patient was discharged on a regimen of oral acyclovir (200 mg, five times a day) and topical trifluridine four times daily.

Case 2

A 25-year-old woman with asthma and atopic dermatitis was examined for a three-day history of pain in the right eye and one day of pain in the left eye. She had a history of labial cold sores, but none in the previous three months. Over the previous three days she had noted malaise, a rash on the chest, and ulcers of the lips and tongue. She was febrile (40.5 C), photophobic, and had tender preauricular lymphadenopathy. The lips were swollen and multi-

ple vesicular lesions were present on the tongue, which also displayed leukoplakia (Fig. 3). A vesicular rash was present on her breasts. Swelling of the eyelids and a marked conjunctival papillary reaction were present bilaterally. An extensive epithelial keratitis with multiple dendritic forms was noted in the right eye (Fig. 4). Punctate epithelial erosions of the left cornea were noted. Corneal sensation of the right eye was diminished. There was no evidence of iridocyclitis. A Tzanck smear of the skin showed multinucleated giant cells, and the results of both conjunctival and skin cultures were positive for herpes simplex virus type 1. A scraping of her tongue disclosed *Candida albicans*.

Eczema herpeticum complicated by herpetic keratoconjunctivitis and oral thrush was diagnosed. She was hospitalized for treatment with intravenous acyclovir (5 mg/kg of body weight every eight hours) and topical trifluridine eyedrops every three hours. She also received clotrimazole troches. Within 24 hours only ghost dendrites were seen. The corneal epithelium had healed completely in 72 hours (Fig. 5). Skin and oral lesions improved gradually with an additional three days of intravenous acyclovir.

Case 3

A 40-year-old homosexual man with severe atopic dermatitis and a diagnosis of AIDS-related complex was examined in the clinic because of a one-day history of irritation of the left eyelid. The patient was monocular and had keratoconus and aphakia. Additionally, he had a history of recurrent herpetic keratitis. The most recent episode occurred two years before the onset of the current problem. The patient was taking oral acyclovir, 200 mg three times daily, as prophylaxis for recurrent herpetic disease. On examination he was found to have a vesicular rash on the left side of the face involving the ophthalmic and maxillary dermatomes and extending from the nose to the pinna of the ear. The patient was afebrile, and there was no evidence of regional lymphadenopathy. The left upper eyelid was swollen and had multiple vesicular lesions. There was a severe conjunctival papillary reaction. Three epithelial dendritic lesions were observed on the left cornea. The oral acyclovir dose was increased to 400 mg five times daily and topical trifluridine eyedrops were begun every three hours.

The next day there was almost complete reso-

lution of the dendrites. The rash had worsened, however, with the appearance of many new vesicles. The results of indirect immunofluorescence of a skin scraping were positive for herpes simplex virus type 1. The patient was admitted for treatment with intravenous acyclovir at a dose of 5 mg/kg of body weight every eight hours and topical treatment with trifluridine was continued. Within 48 hours of hospitalization the keratitis had resolved completely. New skin eruptions, however, continued to appear on the patient's face through the fourth hospital day. The results of direct immunofluorescent staining of a skin scraping taken on the fourth hospital day were positive for herpes simplex virus type 1 as were viral cultures taken at the same time. In vitro testing of the viral isolate disclosed no evidence of resistance to acyclovir. The patient completed ten days of intravenous therapy with acyclovir and was discharged on a regimen of oral acyclovir, 400 mg five times a day. At the time of discharge the skin had cleared and there was no scarring of the cornea.

Discussion

Individuals with atopic disease are at risk for disseminated infection with herpes simplex virus (eczema herpeticum), including severe ocular infection.[12-14] We treated three patients with eczema herpeticum complicated by herpetic keratoconjunctivitis. In each case the diagnosis of eczema herpeticum was based on the patient's history of atopic disease, the presence of a painful disseminated vesicular rash, and positive results of viral cultures for herpes simplex. All three patients had a previous history of recurrent herpetic labial or ocular disease. Common features of the ophthalmic disease included marked ocular discomfort, papillary conjunctivitis, extensive corneal epithelial disease, and prompt response to treatment with systemic acyclovir and topical trifluridine.

The occurrence of disseminated skin and mucous membrane disease in these patients was similar to that which has been previously described in eczema herpeticum, except for several features. First, our patients had relatively mild systemic disease. Second, all three of our patients had a history of recurrent ocular or labial herpetic disease. Finally, our patients were all adults (range, 18 to 40 years of age).

Eczema herpeticum has generally been described as a disease of childhood, which results from primary infection with herpes simplex virus. A recent report from Germany, however, suggests that eczema herpeticum is now being seen with increasing frequency in adults, in whom it represents a form of recurrent disease.[15] Perhaps the older age and previous exposure to the herpesvirus explains the less severe nature of the systemic disease in our patients.

An interesting aspect of one of our cases (Case 3) was development of disseminated disease despite the use of prophylactic acyclovir. Although prophylactic use of oral acyclovir reduces both the number and duration of episodes of genital herpetic disease,[16-18] breakthrough recurrences occur, and the optimal dose for suppressive therapy of recurrent genital infection has not been determined.[19] Furthermore, the serum levels that can be achieved with oral acyclovir are limited.

Little is known about the effectiveness of oral acyclovir for suppression of recurrent ocular herpetic infection. Kaufman and associates[20] reported that treatment with systemic acyclovir had no effect on the frequency of asymptomatic viral shedding in a rabbit model of herpetic ocular disease. However, Schwab[21] reported promising results for the use of long-term systemic acyclovir in patients with severe, recurrent herpetic keratitis and keratouveitis. Of our three cases of eczema herpeticum, the patient who had used suppressive acyclovir therapy exhibited the least severe and least disseminated disease. This was despite concurrent infection with the human immunodeficiency virus. Possibly the severity of this patient's disease was blunted by the use of acyclovir prophylaxis.

Herpetic ocular infection in individuals with atopic disease is often bilateral with extensive corneal epithelial ulceration.[12-14] We found these same characteristics in our patients. Two patients had bilateral disease (Cases 1 and 2), and all three had multiple corneal dendritic ulcers and extensive punctate epitheliopathy. One patient (Case 1) also had a geographic epithelial ulcer. Another feature of herpetic corneal disease in patients with atopic disease is the prolonged course of the disease despite therapeutic intervention.[18] In contrast, healing was rapid in all three of our patients, with complete resolution of epithelial disease within 48 to 72 hours. This was notable for two reasons. First, all three patients had extensive epithelial disease, and second, all three were functionally

Fig. 1 (Margolis and Ostler). Case 1. Facial rash of eczema herpeticum in an 18-year-old woman.

Fig. 2 (Margolis and Ostler). Case 1. Geographic corneal ulcer and multiple small dendrites in a patient with untreated eczema herpeticum.

immunosuppressed as evidenced by their disseminated disease.

There are several possible explanations for the rapid corneal healing in our patients. First, this may simply reflect the natural course of ocular disease in eczema herpeticum. Based on our experience, however, we believe that this is unlikely. Alternatively, the rapid healing of the corneal epithelium in our patients may have been caused by treatment with systemic acyclovir. We also believe that this is unlikely since corneal healing in immunocompetent patients treated with oral or topical acyclovir takes an average of five to seven days.[22-26] We cannot rule out, however, the possibility of more rapid healing in response to intravenous administration of this drug.

The most likely explanation for the rapid

Fig. 3 (Margolis and Ostler). Case 2. Vesicular herpetic ulcers of the lips and tongue in a patient with untreated eczema herpeticum. Also note the leukoplakia of the tongue caused by *Candida albicans*.

Fig. 4 (Margolis and Ostler). Case 2. Multiple corneal dendrites in a patient with untreated eczema herpeticum.

Fig. 5 (Margolis and Ostler). Case 2. Healed corneal epithelium three days after initiating therapy of intravenous acyclovir and topical trifluridine.

corneal epithelial healing in our patients was the combined use of systemic acyclovir and topical trifluridine. This is supported, in part, by our observation that the epithelial keratitis of all three patients resolved much more rapidly than did the skin or mucous membrane lesions treated by acyclovir alone. Furthermore, in at least one of our patients (Case 3) vesicles confirmed by cultures continued to erupt at nonocular sites for two days after resolution of the corneal dendritic ulcers. In vitro studies have demonstrated the additive, albeit nonsynergistic, effects of acyclovir and trifluridine.[27] It is possible that by using these two drugs in combination we were able to obtain a level of antiviral activity in the cornea not achieved by either drug alone.

Based on the observations of the rapid healing of herpetic keratitis in these three patients, we recommend the use of systemic acyclovir and topical trifluridine in all cases of eczema herpeticum complicated by herpetic keratoconjunctivitis. Although all three of our patients were treated with intravenous acyclovir, the results of a recent double-masked clinical trial[11] indicate that oral acyclovir is also effective in the treatment of eczema herpeticum. Since administration of oral acyclovir (400 mg, five times a day) results in aqueous humor and tear film drug levels above the mean 50% inhibitory dose for herpes simplex virus,[25,28] treatment with oral acyclovir and topical trifluridine may also be effective in the treatment of the ocular disease of patients with eczema herpeticum. We similarly recommend therapy with oral acyclovir and topical trifluridine for any individuals with atopic disease and herpes simplex keratitis.

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Oᴘʜᴛʜᴀʟᴍɪᴄ ᴍɪɴɪᴀᴛᴜʀᴇ

Anyway, last week all of a sudden the pupil of my big gorgeous left eye got twice as big as it should be, and they have been checking and testing and giving me glassy smiles, and I am mailing this en route to the place where they are going to open a trap door and take another look.

John D. MacDonald, *Pale Gray for Guilt*
New York, Ballantine Books, 1982, p. 221

Ocular Findings in Treacher Collins Syndrome

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and Rosalie B. Goldberg, M.S.

We examined 14 patients from nine families referred with the diagnosis of Treacher Collins syndrome. We noted seven significant ocular findings including the following: a subnormal horizontal palpebral fissure length and inferomedial displacement of the lateral canthus in primary gaze; further medial displacement (4.0 mm or more) of the lateral canthus with resultant shortening of the horizontal fissure length on forced eyelid closure (fissure narrowing sign); partial-thickness eyelid colobomata localized to the nasal one half to two thirds of the lower eyelids; bilateral absence of the inferior lacrimal puncta; bilateral blepharoptosis; inferior displacement of the palpebral fissures; and regular astigmatism without any consistent orientation of the axis of astigmatism relative to the lower eyelid defects, blepharoptosis, or lateral canthus. The fissure narrowing sign correlates with known anatomic deficiencies in the Treacher Collins syndrome and may prove valuable in confirming the diagnosis in patients who lack certain typical features.

THE TREACHER COLLINS SYNDROME is a rare, genetically transmitted congenital malformation syndrome, involving primarily the facial bones. It is inherited as an autosomal dominant trait with variable expressivity. The chief features of this syndrome include the following: hypoplasia of the facial bones, especially the malar bone and mandible; antimongoloid slant of the palpebral fissures; malformation of the auricles with external ear canal defects and frequent conductive deafness; notching or colobomata of the outer portions of the lower eyelids and, more rarely, the upper eyelids; deficient cilia along the medial two thirds of the lower eyelids; macrostomia, a high-arched palate, and malocclusion of the teeth; blind fistulae or dimples between the angles of the mouth and the ears; atypical, tongue-shaped projections of the hairline toward the cheeks; and other associated anomalies, including skeletal deformities and facial clefts[1] (Fig. 1).

The ophthalmic literature includes over 30 reports of Treacher Collins syndrome, each discussing one or two isolated cases or multiple cases in a single family. There are several literature reviews,[1,2] but no prospective series of unrelated and previously unreported patients.

Patients and Methods

The study sample was composed of 14 patients from nine families (five males and nine females) with the diagnosis of Treacher Collins syndrome, selected from the computerized files of the Center for Craniofacial Disorders of Montefiore Medical Center. Diagnostic criteria included the results of extensive cephalometric and genetic analyses, including complete family pedigrees. Patients' ages ranged from 1 week to 45 years. Two patients had undergone at least one previous plastic surgical procedure to correct facial and orbital deformities. Patients were examined in two sessions. A complete ocular examination was performed on each patient, including Hertel exophthalmometry, keratometry, slit-lamp examination, cycloplegic refraction, and fundus examination with a dilated pupil.

Anthropometric measurements taken with a sliding calipers included the horizontal palpebral fissure length in primary gaze and on forced eyelid closure, the vertical palpebral fissure length, the intermedial canthal distance, the vertical distance from the lateral canthus to an extended intermedial canthal line, the dis-

Fig. 1 (Wang and associates). An 8-year-old girl with Treacher Collins syndrome. Left, Frontal view. The antimongoloid obliquity of the palpebral fissures and hypoplasia of the malar bones are particularly evident. Right, Lateral view. Note the malformed, low-set auricle and micrognathia.

tance from the upper eyelid margin to the pupillary light reflex, the interpupillary distance, and the distance through which the upper eyelid margin moves on going from downgaze to upgaze (levator palpebrae function).

Each patient was also examined for anatomic defects of the eyelids, lagophthalmos, presence and patency of the lacrimal puncta, displacement or absence of the lateral canthal tendon, facial asymmetry, and malar hypoplasia. Photographs of each patient were taken for photogrammetric analysis. Anatomic landmarks and techniques of measurement have been previously described.[3]

The anthropometric data obtained were compared to population norms.[4-6] A value greater than 2 S.D. from the mean for any given measurement was considered abnormal. A decrease in the horizontal palpebral fissure length of 4.0 mm or more on forced eyelid closure was regarded as a positive fissure narrowing sign. We determined this by measuring the horizontal palpebral fissure length in 100 normal patients of varying ages (range, 1 week to 70 years) without eyelid or adnexal disease. Narrowing of the horizontal palpebral fissure on forced eyelid closure was less than 2.0 mm in all patients older than 7 years of age and less than 1.0 mm in all patients 7 years of age or younger. A value of 4.0 to 4.5 mm or less was considered subnormal for the distance between the upper eyelid margin and the pupillary light reflex.[3]

Results

The horizontal palpebral fissure length was subnormal in nine patients, including six patients older than 7 years of age and three patients 7 years of age or younger (Cases 2, 3, and 8). Forced eyelid closure resulted in a more pronounced narrowing of the horizontal palpebral fissure length in all of these patients, which we described as the fissure narrowing sign. Horizontal fissure length values are given in the Table (normal control subjects: mean, 31.0 mm [range, 28.0 to 32.0 mm] for patients older than 7 years of age, and mean, 20.0 mm [range, 17.0 to 21.0 mm] for patients 7 years of age or younger). In all nine patients, the lateral canthal tendon was absent on external examination, as determined by digital deviation of the lateral canthus nasally. In no patient was the fissure narrowing sign present without a short horizontal palpebral fissure length in primary gaze and vice versa.

The eyelids showed several consistent abnormalities in the seven most severely affected patients. Notching or full-thickness defects were not found, nor was there any previous surgery to repair such an abnormality. Partial-thickness defects were, however, identified. The tarsal plates were much reduced or completely absent in the medial one half to two thirds of the lower eyelids. Skin and conjuncti-

TABLE

HORIZONTAL PALPEBRAL FISSURE LENGTHS (MM) IN NINE PATIENTS WITH THE FISSURE NARROWING SIGN

PATIENT NO.	EYE	EYELID POSITION		FISSURE LENGTH DECREASE
		OPEN	FORCED CLOSURE	
1	R.E.	22.0	19.0	3.0
	L.E.	20.0	16.0	4.0
2	R.E.	20.0	16.0	4.0
	L.E.	20.0	16.0	4.0
3	R.E.	21.0	15.5	5.5
	L.E.	21.0	15.5	5.5
4	R.E.	28.5	24.0	4.5
	L.E.	29.0	25.0	4.0
5	R.E.	20.0	15.0	5.0
	L.E.	20.0	15.0	5.0
6	R.E.	23.0	19.0	4.0
	L.E.	23.0	19.0	4.0
7	R.E.	22.0	17.0	5.0
	L.E.	24.0	18.0	6.0
8	R.E.	20.0	15.0	5.0
	L.E.	20.0	15.0	5.0
9	R.E.	28.0	22.0	6.0
	L.E.	28.0	22.0	6.0

va overlying these regions were intact, but cilia were consistently absent along the margins. In all seven patients these defects were bilateral and symmetric. The contour of the lower eyelids demonstrated a characteristic "S"-shaped configuration in the five patients with no previous eyelid surgery. The palpebral apertures had an antimongoloid obliquity with a rounded, inferomedially displaced lateral canthus. The inferior lacrimal punctum was absent bilaterally in five of the seven patients. In the patient with the most severe expression of the syndrome, the superior puncta were absent as well.

The distance from the upper eyelid margin to the pupillary light reflex and the vertical palpebral fissure length were both subnormal in six patients. Five others had a subnormal distance between the upper eyelid margin and the pupillary light reflex with a normal vertical palpebral

fissure length. In two severely affected patients, previous surgery of the eyelids and orbital region precluded true assessment of these variables, with the distance between the upper eyelid margin and the pupillary light reflex and vertical palpebral fissure length both falling within the normal range.

A supernormal intermedial canthal distance was found in only one patient. Lagophthalmos and an increased interpupillary distance were each found in three patients. Sclera visible beneath the inferior corneoscleral limbus with the eye in primary position (scleral show) was identified in seven patients. Facial asymmetry was noted in eight patients, and 11 patients were found to have significant malar hypoplasia.

Cycloplegic refraction disclosed a refractive error requiring spectacle correction in 12 patients. Regular astigmatism of greater than 2.00 D was found in five patients. The mean and median astigmatism in these five patients was 4.38 D and 4.75 D, respectively. The axis of the negative cylinder was usually in the quadrant of the horizontal palpebral fissure axis (for example, ranging from 15 to 80 degrees in the right eye). There was an overall correlation between the severity of facial and eyelid abnormality (malar hypoplasia, absent lateral canthal tendon with downward displacement, and nasal lower eyelid deficiency) and the presence of astigmatism. In two patients, the astigmatism was unilateral. In only one of these two patients was the facial and eyelid abnormality more severe on the side with the astigmatism. There were other patients with similar facial asymmetry without astigmatism. Keratometry disclosed differences in the corneal radius of curvature along axes approximating the astigmatic axes in each case. Significant anisometropia (greater than 1.50 D of spherical or cylindrical difference) was identified in eight patients.

Discussion

The Treacher Collins syndrome is a specific type of mandibulofacial dysostosis inherited as an autosomal dominant trait. The syndrome was first described by Berry in 1889,[7] who reported a mild expression in a mother and daughter. His cases demonstrated two of the most commonly reported ophthalmologic findings in the disorder, namely colobomata in the temporal aspect of the lower eyelids and an

antimongoloid obliquity of the palpebral fissures. In 1900, Treacher Collins[8] published two additional case reports describing a more complete and characteristic expression of the syndrome in which marked hypoplasia of the malar bones contributed significantly to the abnormal facies.

Pires de Lima and Monteiro[9] described two brothers with a severe expression of the syndrome and postulated a disturbance in branchial arch development as a cause of the observed defects. Mandibular hypoplasia, external ear deformities, rectangular upward deviation of the lateral portion of the lower eyelids, and a mild facial asymmetry were added to the classic triad of anomalies elucidated by Treacher Collins.

Absence of the lateral canthal tendon, a known anatomic deficiency in Treacher Collins syndrome, contributes significantly to many of the characteristic facial features. Hypoplasia of

the malar bones (more specifically the frontal process of the zygomatic bone, which comprises the inferotemporal orbital rim) may be the primary anatomic defect, which leads to failed development of the attachment site for the lateral canthal tendon.[4] Mild hypoplasia to aplasia of the frontal process of the zygoma has been identified in a series of 14 patients with Treacher Collins syndrome by using three-dimensional osseous surface reformation imaging from computed tomographic scans.[10] The frontal process was noted to be the most consistently and seriously deformed portion of the zygoma.

The lack of lateral canthal fixation results in narrowing of the horizontal palpebral fissure in primary gaze and inferomedial displacement and rounding of the lateral canthus. Bachelor and Kaplan[11] described two patients with Treacher Collins syndrome who had surgically confirmed absence of the lateral canthal ten-
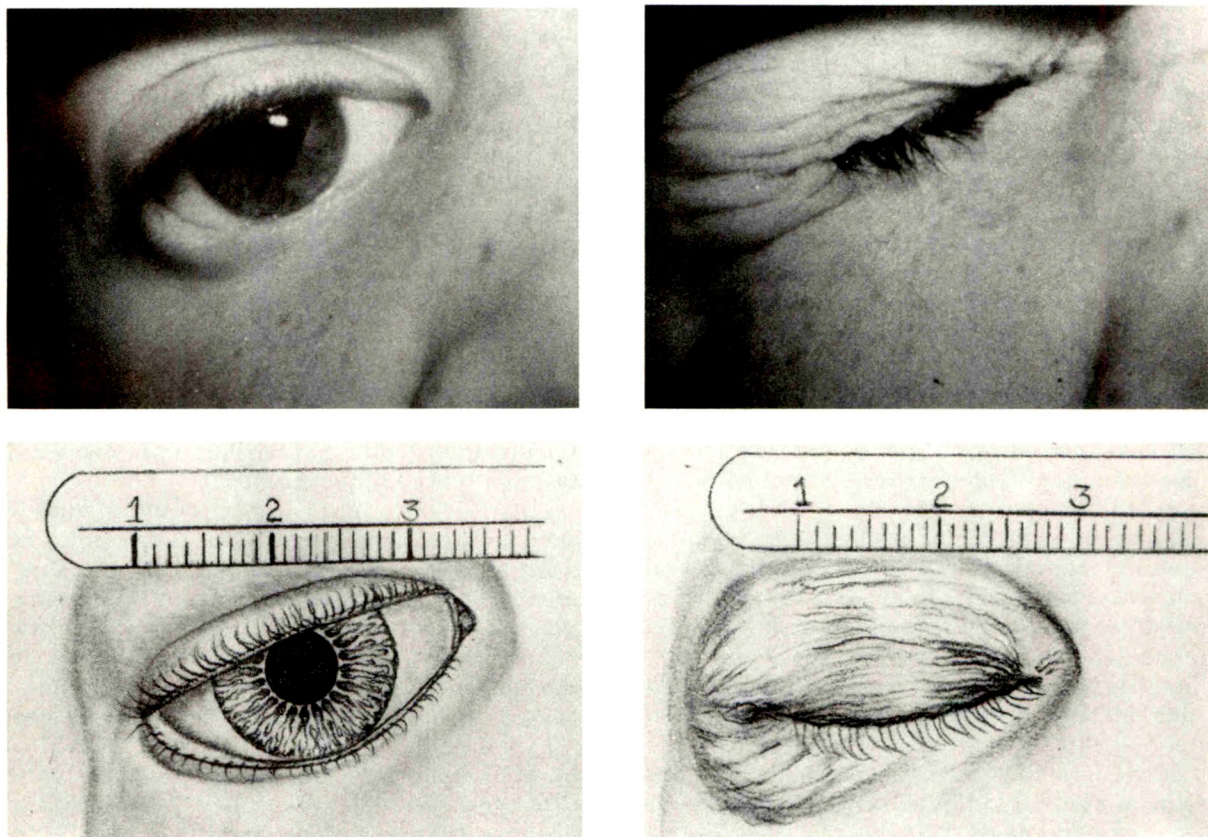
Fig. 2 (Wang and associates). Right eye of an 8-year-old girl with Treacher Collins syndrome. Top left, Photogrammetric representation with the eye open in primary gaze. Top right, Marked narrowing of the palpebral fissure is observed on forced eyelid closure as the sphincteral action of the orbicularis oculi pulls the lateral canthus medially. Bottom left, Schematic representation, eye open. Bottom right, Schematic representation, forced closure.

don. In both cases, they noted drooping of the lower eyelids and a medial displacement of the lateral canthus, which was increased on active eyelid closure (fissure narrowing sign). Horizontal shortening of the fissure occurs with forced eyelid closure since the lateral canthal sling is not anchored to the temporal orbital rim. Sphincteral contraction of the orbicularis oculi pulls the lateral canthus medially in the absence of lateral fixation (Fig. 2). The 4.0-mm limit for designating fissure narrowing as an abnormality should allow for normal physiologic variation and systematic error in measurement.

The nine most severely affected patients in the present study had a fissure narrowing sign. In the five patients with more mild expressions and the fewest significant ocular findings, the sign was absent. There are no minimal diagnostic criteria for Treacher Collins syndrome and mildly affected individuals are sometimes missed. The fissure narrowing sign may thus prove useful in confirming the diagnosis of Treacher Collins syndrome, especially in patients who fail to exhibit many of the more typical features. We do not, however, have sufficient data to conclude that its absence excludes the diagnosis. Because there is no definitive diagnostic test, such as a specific DNA marker or an identifiable gene locus, we could speculate that the five patients with the fewest ocular findings may have a mandibulofacial dysostosis, but not Treacher Collins syndrome.

The published reports of Treacher Collins syndrome are replete with references to colobomata in the temporal portion of the lower eyelids. This defect is reported to occur in 69% of affected individuals.[8] Upper eyelid colobomata have been identified more rarely. In the present study, full-thickness colobomata, manifested as indentations or notching of the eyelid margins, were not found. The absence of the lateral canthal tendon results in an "S"-shaped lower eyelid contour, an antimongoloid slant, and a trapezoidal shape to the palpebral aperture. The false appearance of temporal lower eyelid colobomata is thus created in the absence of true full-thickness defects. Former references to such anomalies were probably descriptions of the unsupported lateral canthus that droops at its temporal aspect.

Mann[12] provides a detailed description of the eyelid anomalies in a patient with Treacher Collins syndrome. The medial portion of the lower eyelid was thin, atrophic, and devoid of all marginal structures, including eyelashes and meibomian glands. Such a partial-thickness dysgenesis, comprising a deficient tarsal plate, meibomian glands, and cilia with intact overlying skin and conjunctiva, has been described in several other case reports,[1,2,8] typically occurring in the medial one half to two thirds of the lower eyelids. In our study, bilateral absence of the tarsus and cilia in the medial portion of the lower eyelids was common in the more severely affected patients.

The association of Treacher Collins syndrome with bilateral atresia of the lower lacrimal punctum and canaliculus has been reported.[13,14] Bilateral absence of the inferior lacrimal punctum was a common finding in our patients. This defect was always associated with the tarsal and ciliary deficiencies, which suggests failed development of components of the medial lower eyelids and not a full-thickness fusional defect. Only the most severely affected patients had this anomaly.

Reduction in both the vertical palpebral fissure length and the distance between the upper eyelid margin and the pupillary light reflex, which indicates blepharoptosis, was found in six patients. A subnormal distance between the upper eyelid margin and the pupillary light reflex with a normal vertical palpebral fissure length, which indicated an inferior displacement of the entire palpebral fissure and a normally positioned globe, was found in five patients (Fig. 3). Mann[12] had described a downward droop of the upper eyelids at their temporal aspect, which led to an eccentric positioning of the globe with respect to the palpebral aperture. Absence of the lateral canthal tendon and malar hypoplasia results in sagging of the unsupported lateral canthus and downward traction on the upper eyelid.

Kolar, Farkas, and Munro[15] studied surface structure in Treacher Collins syndrome by using a variety of anthropometric measurements. They identified a supernormal intermedial canthal distance consistent with hyperteloric orbits in 72% of the patients examined. In the present study, a supernormal intermedial canthal distance was found in only one patient.

Experimentally induced soft tissue anomalies in rabbits, such as eyelid colobomata proximate to the corneoscleral limbus, have been shown to produce changes in the corneal curvature resulting in astigmatic refractive errors.[16] The axis of astigmatism in these experimental cases was related to the position of the soft tissue anomaly. No change in central keratometry readings was detected. Direct comparison of these re-
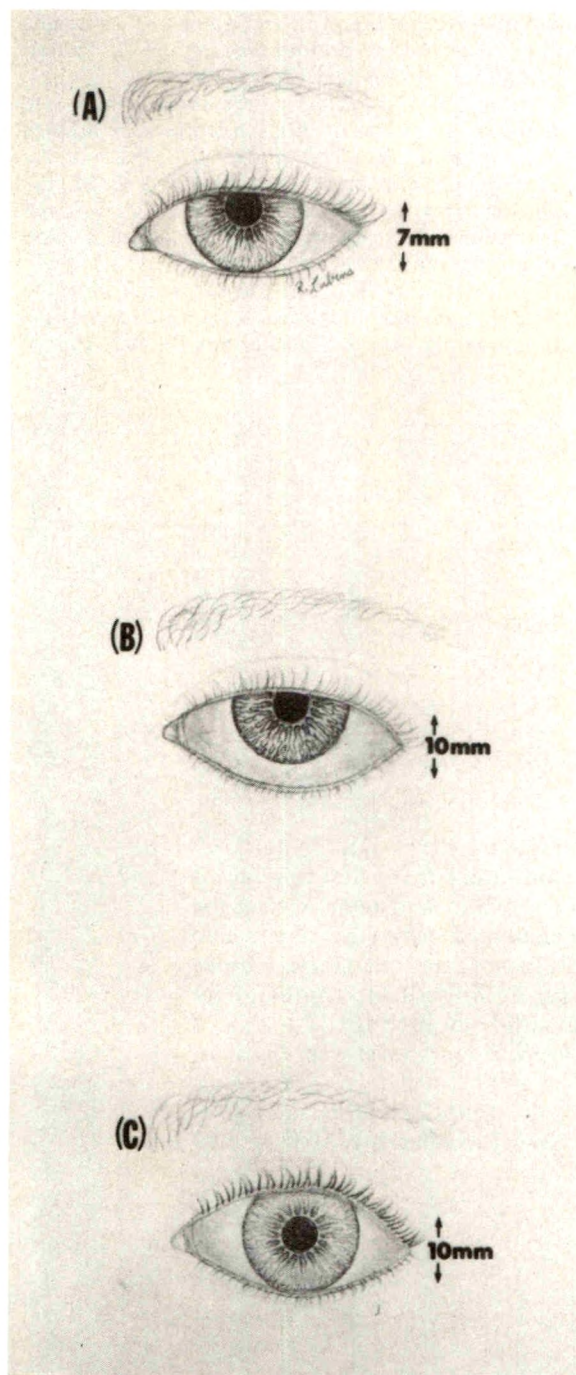
Fig. 3 (Wang and associates). Top, Right eye of a patient with a blepharoptotic upper eyelid. Both the distance from the upper eyelid margin to the pupillary light reflex and the vertical palpebral fissure length are decreased. Middle, Right eye of a patient with an inferiorly displaced palpebral fissure. The vertical palpebral fissure length is normal, whereas the distance from the upper eyelid margin to the pupillary light reflex is decreased. Bottom, Normal right eye in primary gaze.

sults to the present study cannot be made since full-thickness colobomata were not observed in our patients. The astigmatic errors we found bore a rough axial relationship to some of the soft tissue defects noted. Central keratometry readings in our study did verify the astigmatism to be of corneal origin.

Significant anisometropia was present in most patients. Although this has been associated with problems of periorbital asymmetry (hemangiomas[17,18] and blepharoptosis[18]), no good correlation between refractive and anatomic asymmetry was found in our patients. The relationship between the eyelid abnormalities and refractive errors in the present study remains unclear.

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OPHTHALMIC MINIATURE

Miller looked into his eyes and saw . . . nothing. For the first time in his life, Sean Miller knew fear. He saw his own death, and remembered the long-past lessons in Catholic school, remembered what the sisters had taught him, and his fear was that they might have been right. His face broke out in a sweat and his hands trembled as, despite all his contempt for religion, he feared the eternity in hell that surely awaited him.

Ryan saw the look in Miller's eyes, and knew it for what it was. *Goodbye, Sean. I hope you like it there . . .*

Tom Clancy, *Patriot Games*
New York, Berkley, 1988, p. 497

Accommodative Convergence in Hypermetropia

Gunter K. von Noorden, M.D., and Cynthia W. Avilla, B.S.

We compared the clinical characteristics of esotropic, hypermetropic children whose strabismus was fully corrected with spectacles (refractive accommodative esotropia) with those who remained orthotropic (that is, had no manifest strabismus on the cover test) in the presence of uncorrected hypermetropia. In addition to a standard ophthalmologic and orthoptic examination, we determined the stimulus accommodative convergence/accommodation (AC/A) ratio by using the gradient method over a range of 6 diopters, the near point of accommodation, and random dot stereopsis. Hypermetropic patients without esotropia or significant esophoria were found to have a low AC/A ratio in contrast to those patients with refractive accommodative esotropia. This finding explains why esodeviations may be absent in some hypermetropic patients with uncorrected vision. We found a high prevalence of abnormally low near points of accommodation and defective or absent stereopsis in both groups of patients.

THE RELATIONSHIP between esotropia and hypermetropia has been established ever since Donders made his classic contribution in 1864.[1] In his treatise, Donders asserted that strabismus may be absent in those with severe hypermetropia and speculated that such patients do not make the effort to accommodate sufficiently to clear their blurred retinal images. Donders suggested that if such patients would exert accommodation in accordance with their severe hypermetropia, esotropia would develop.

We had on several occasions, however, encountered patients with uncorrected hypermetropia who had to make a great accommodative effort to have a visual acuity of 20/20. These patients, however, remained essentially orthotropic at near and distance fixation or developed only insignificant amounts of esophoria. This observation, which is in apparent contrast with Donders' teachings, led us to study this unusual response.

Subjects and Methods

Between 1973 and 1989, we studied nine consecutive, alert, and cooperative patients (Group A) who fulfilled the following criteria: no history of esotropia or any other form of strabismus, no previous optical correction of a hypermetropia of +4.00 diopters or more, absence of anisometropia of more than 1.50 diopters, and orthotropia or esophoria of less than 10 prism diopters at near or distance fixation without spectacles on an accommodative fixation target. None of the patients had worn spectacles previously, and uncorrected visual acuity at distance was 20/30 or better with each eye in all but one patient (Case 2) whose visual acuity was R.E.: 20/50 and L.E.: 20/40. The ages of these patients ranged from 5 to 16 years at the time of the first examination (mean, 7.8 years). The mean refractive error was +7.52 diopters (range, +4.25 to +15.00 diopters) in the right eye and +7.51 diopters (range, +4.00 to +15.00 diopters) in the left eye. In addition to a complete ophthalmologic examination, which included an orthoptic work-up, data on stimulus accommodation convergence/accommodation (AC/A) ratio, near point of accommodation, and stereoacuity were obtained.

A cycloplegic refraction was performed, and the full refractive error was prescribed. After the spectacles had been worn for at least six weeks, the stimulus AC/A ratio was measured with the gradient method[2] by clipping spherical lenses ranging from −3.00 to +3.00 diopters in

1-diopter steps on the patient's spectacles. The heterophoria or heterotropia induced by the lenses was measured with the prism cover test while the patient fixated on an accommodative target at a viewing distance of 33 cm. The AC/A ratio was computed by dividing the change in horizontal heterophoria in prism diopters by the change in stimulus to accommodation in diopters (prism diopters/diopters [p.d./D]).

The near point of accommodation was determined with the Prince rule while the patient was wearing the full hypermetropic correction. An accommodative target (20/30 letter) was moved toward the patient along the ruler until the patient reported blurring. Several determinations were made, and the average distance at which blurring occurred was recorded in diopters. Stereopsis was measured with the TNO random dot stereo test.

A control group (Group B) consisted of 30 consecutive patients with refractive accommodative esotropia, that is, the patients' esotropia was completely corrected by spectacles at near and distance fixation. Of these children, 29 had a corrected visual acuity of 20/40 or better. One patient (Case 1) had a visual acuity of R.E.: 20/50 and L.E.: 20/40. The patients' ages ranged from 6 to 13 years (mean, 11.6 years). The mean refractive error was +5.64 diopters (range, +3.50 to +9.25 diopters) in the right eye and +5.75 diopters (range, +3.75 to +9.50 diopters) in the left eye. All patients in Group B had a constant esotropia without their spectacles at near and distance fixation and had been esotropic for varying periods before the prescription of their first spectacles. One patient (Case 15) had a microtropia, and the other patients were orthotropic or had a well-controlled esophoria with spectacles.

Results

The AC/A ratio in patients from Group A (Table 1) was found to be either reduced or its slope to be completely flat (Cases 5 and 9), in which case no significant phoria response could be evoked by adding plus and minus spherical lenses to the patient's spectacles. In other words, there was no apparent synkinesis between accommodation and convergence. The mean AC/A ratio in Group A was 1.53 p.d./D (range, 0 to 2.6 vs 4.19 p.d./D (range, 1.1 to 9.0 p.d./D in Group B (Table 2). This difference was statistically significant (t-test, P < .001).

The results of measurements of the near point of accommodation in Group A and Group B are compared in the Figure with the upper and lower limits of normal near points of accommodation as established by Duane.[3] Perhaps coincidentally, abnormally low near points were more frequently encountered in the right eye than in the left eye. The near points of all right eyes were chosen to display the variations from the normal range. According to Duane,[3] a near point of accommodation of less than 10 diopters in the age group under consideration (5 to 14 years) must be considered abnormally low. Two of eight patients from Group A had an abnormally low near point in one eye (Cases 1 and 2), and two had a reduced near point in both eyes (Cases 5 and 9) (Table 1). Of 30 children from Group B, ten had

TABLE 1
CLINICAL CHARACTERISTICS OF PATIENTS IN GROUP A

CASE NO., AGE (YRS)	REFRACTION R.E.	REFRACTION L.E.	VISUAL ACUITY R.E.	VISUAL ACUITY L.E.	NPA (D)* R.E.	NPA (D)* L.E.	AC/A	STEREOPSIS (SEC)
1, 7	+15.00	+15.00	20/30	20/30	6	10	2.3	240
2, 6	+13.00 + 1.00 × 95	+13.00 + 1.00 × 80	20/50	20/40	8	10	1.3	1,980
3, 5	+5.50	+5.75 + 0.25 × 30	20/30	20/25	Not tested		2.3	Nil
4, 8	+4.75	+4.75	20/20	20/20	13	13	2.6	Nil
5, 9	+7.00	+6.00	20/30	20/20	3	8	Absent	Not tested
6, 5	+4.25	+4.00	20/20	20/20	14	15	2.1	60
7, 16	+4.00 + 0.50 × 105	+3.75 + 0.50 × 40	20/20	20/20	10	10	1.6	15
8, 7	+6.50	+7.50	20/25	20/30	14	14	1.6	60
9, 8	+7.00	+7.00	20/20	20/20	9	9	Absent	240

*NPA indicates near point of accommodation.

TABLE 2

CLINICAL CHARACTERISTICS OF PATIENTS IN GROUP B

CASE NO., AGE (YRS)	NPA (D)* R.E.	NPA (D)* L.E.	AC/A	STEREOPSIS (SEC)
1, 7	8	9	1.1	1,980
2, 22	9	9	6.8	Nil
3, 6	11	9	4.5	120
4, 8	9	10	4.1	120
5, 6	15	15	4.1	240
6, 8	8	9	3.8	30
7, 10	7	9	3.1	60
8, 10	12	12	3.5	60
9, 8	12	14	2.1	Nil
10, 9	11	10	4.3	Nil
11, 6	18	18	3.0	Nil
12, 9	12	12	5.6	Nil
13, 13	11	12	2.3	Nil
14, 7	11	11	8.0	240
15, 8	12	13	3.0	Nil
16, 12	11	12	6.3	30
17, 6	15	15	4.6	240
18, 8	12	12	3.0	Nil
19, 8	9	8	9.0	240
20, 6	10	10	4.3	Nil
21, 12	8	9	4.8	Nil
22, 13	8	9	3.8	240
23, 9	8	9	4.8	1,980
24, 7	12	10	1.3	1,980
25, 6	12	12	1.5	1,980
26, 8	11	9	3.3	60
27, 9	10	12	5.0	240
28, 9	13	14	5.6	1,980
29, 12	11	12	5.3	60
30, 10	10	11	4.0	120

*NPA indicates near point of accommodation.

abnormally low near points of accommodation in one (Cases 3, 4, and 26) or both eyes (Cases 1, 6, 7, 19, 21, 22, and 23).

Four patients (Cases 1, 2, 5, and 9) from Group A and one patient (Case 1) from Group B had reduction of both AC/A ratio and near point of accommodation, but no correlation between these two measurements existed in the remainder of the patients from Groups A and B.

Stereopsis was considered to be decreased when it was measured to be less than 240 seconds of arc.[4] Reduced stereopsis or stereoblindness was recorded in five of eight patients from Group A whose stereopsis was tested and in 21 of 30 patients from Group B. Thus, reduced or absent stereopsis was a feature that occurred frequently in patients with severe hy-

permetropia with and without refractive accommodative esotropia.

We found no relationship between reduced stereopsis and a reduced near point of accommodation because we studied stereoblind patients with a normal near point of accommodation (Group A, Case 4; Group B, Cases 9 to 13, 15, 18, and 20) and those with reduced near points of accommodation and normal stereopsis (Group B, Cases 6 and 7). Likewise, no relationship was seen between visual acuity at near and reduced stereopsis because visual acuity at near, though not tested in all patients, was normal (J1) in patients with reduced stereopsis (Group B, Cases 15, 18, 20, and 21).

Discussion

According to Donders,[1] uncorrected hypermetropia may cause esotropia because of excessive accommodation. Donders also realized, however, that only a comparatively small number of esotropic patients develop hypermetropia and suggested that fusion preserves most hypermetropic individuals from strabismus. If accommodative convergence is compensated for by fusional divergence, one would expect such patients to have a significant degree of esophoria at near and distance fixation. The patients from Group A, however, were orthotropic or had esophorias of less than 10 prism diopters.

The data from Group A show that a low AC/A ratio must be added to excessive accommodative convergence and the range of motor fusion amplitudes as a factor that determines whether a hypermetropic individual becomes esophoric or esotropic or remains orthotropic. These patients were orthotropic or had only insignificant amounts of esophoria without spectacles despite excessive accommodation required to recognize the fixation target used during measurement of the near deviation.

It has been determined that the normal values for the AC/A ratio range from 2.76 p.d./D to 4.50 p.d./D, depending on the methods used.[5] The mean AC/A ratios obtained in Group A must be considered abnormally low and those from Group B as within the normal range.

The stimulus method[6] to determine the AC/A ratio is used widely in clinical work.[2,5] As suggested by Alpern, Kincaid, and Lubeck,[6] however, one disadvantage of this method is the
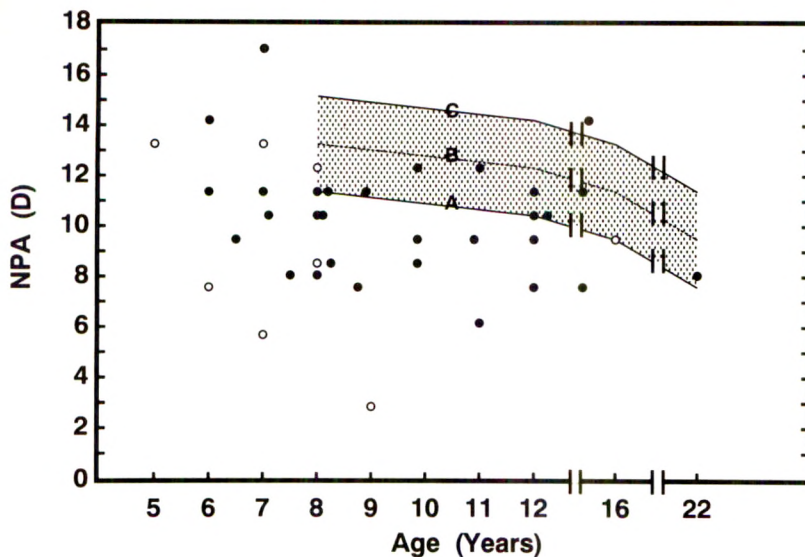
Figure (von Noorden and Avilla). Near point of accommodation in relation to age. Open circles indicate patients in Group A; solid circles, patients in Group B; stippled area, normal range; A, lowest values; B, average values; and C, highest values.

difficulty in determining the state of the patient's accommodation when plus or minus lenses are placed before the eyes. It is planned to measure the response AC/A ratio, that is, the AC/A ratio related to the accommodative response in a suitable subject to corroborate our findings even though a predictable increase of the response AC/A ratio of 8%[6] would not change the significance of our data.

We must ask whether the reduced AC/A ratio in Group A is a primary, innate, or a secondary phenomenon. This question becomes moot if one shares the view of many investigators who consider the stimulus AC/A ratio as a stable, genetically determined relationship between accommodation and convergence, based on a fixed central nervous system arrangement that remains immutable until the presbyopic age or throughout life.[7-11] If one agrees with Helmholtz,[12] however, that the association between accommodation and convergence is a learned process, the possibility must be considered that certain individuals with uncorrected severe hypermetropia fail to make the sustained accommodative effort necessary to focus and consequently develop a low AC/A ratio. In that case, we would expect a good correlation between a low AC/A ratio and a reduced near point of accommodation. With the exception of Cases 1, 2, 5, and 9 from Group A and Case 1 from Group B, however, such a correlation did not exist in the remainder of our patients. For this reason and because of the studies cited, we are inclined to favor the first theory and suggest that an intrinsically low AC/A ratio may pro-

tect certain patients with uncorrected hypermetropia from developing esotropia or esophoria.

The finding of a reduced near point of accommodation in hypermetropic patients with and without strabismus is of interest. Low near points of accommodation have been described in connection with ametropic amblyopia in patients with severe hypermetropia.[13,14] It has even been suggested that one of the possible causes of ametropic amblyopia is a reduced near point of accommodation.[13] Reduced near vision in the presence of normal distance vision, however, is not a recognizable amblyopiogenic factor, and with the exception of Case 2, none of our patients with a reduced near point was amblyopic. Rather, we suggest the possibility that patients with uncorrected hypermetropia do not fully accommodate at all times during infancy. The resulting hypoaccommodative state may eventually cause a reduced accommodative range, perhaps even a disuse atrophy of the ciliary muscle. Although this hypothesis remains unsupported, we have no better explanation for a reduced near point of accommodation in more than one third of our patients. We did not determine the pupillary near response in those with reduced near points to explore whether there are other anomalies of the near reflex in such patients.

The finding of reduced or absent stereopsis as a common feature in patients with moderate or severe hypermetropia was unexpected. Reduced or absent stereopsis was not consistently associated with a reduced near vision from a reduced near point of accommodation. We were

also unable to associate the age at which the hypermetropia was optically corrected and the esodeviation was controlled with spectacles with the sensitivity of stereopsis. We believe, however, that the reduced stereopsis in Group B might be explained on the basis of varying periods of esotropia that were present before the wearing of corrective lenses. It is well known from clinical experience[15] and animal experiments[16,17] that disruption of binocular vision during visual immaturity will cause a permanent defect of stereopsis. It will be of interest to explore whether the defect of stereopsis in patients with refractive accommodative esotropia can be correlated with optokinetic asymmetry, which is another sign of early disruption of binocular vision.[18-20]

Reduced stereopsis in five of the eight patients tested in Group A must be caused by a different mechanism because none of the children we studied had manifest strabismus or a history of such. What these patients may have had in common, however, was a period of blurred form vision in both eyes before optical correction of their hypermetropia. Defective stereopsis has been reported after bilateral form vision deprivation from patching of infants.[21-23] We have also learned from experiments in infant monkeys that a reduction in the number of cortical binocular neurons (which are necessary for stereopsis[24]) is not only caused by artificial strabismus,[25,26] anisometropia,[27] and unilateral eyelid closure,[25] but occurs also after bilateral and symmetric deprivation of form vision.[28] It is reasonable to assume, therefore, that the blurring of vision during infancy before the wearing of spectacles caused deprivation of form vision, loss of cortical binocular function, and thus a reduction or loss of stereopsis in most patients from Group A. It is of interest that a mild ametropic amblyopia was present in only one of these patients (Case 2), which suggests that stereopsis is a visual function more sensitive to the effects of bilateral visual deprivation than visual acuity. This observation is in accord with recent data from our animal laboratory that show that only brief periods of bilateral form vision deprivation in visually immature monkeys suffice to cause a decrease of stereopsis without significantly affecting monocular visual acuity.[28]

To avoid the visual deprivation effect of uncorrected hypermetropia in excess of four diopters on the immature visual system, to improve near vision in those with a reduced near point of accommodation, and to preserve stereopsis, we recommend optical correction in children under the age of 4 years, even in the absence of a manifest or latent esodeviation.

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OPHTHALMIC MINIATURE

"Stand still and shut your eyes for a moment," commanded Miss Brandon's voice from the bed, "and then you'll be able to see. I can't have the blinds up. My eyes are bad."

Mrs. Brandon obediently halted, shut her eyes, and presently opened them again. The gloom was now less dense to her sight and without difficulty she reached the chair placed by the bedside.

Angela Thirkell, *The Brandons*
London, The Hogarth Press, 1988, p. 37

A Comparative Study of Grating and Recognition Visual Acuity Testing in Children With Anisometropic Amblyopia Without Strabismus

David S. Friendly, M.D., Mohamad S. Jaafar, M.D., and Dora L. Morillo, C.O.T.

Bailey-Lovie-Ferris visual acuity charts and Teller visual acuity cards were used to compare recognition and grating visual acuity at near testing distances in 32 children with anisometropic amblyopia without strabismus. Appropriate optical corrections were worn. Test-retest intraobserver reliability was higher for letters ($r = .95$) than for gratings ($r = .68$). Using 20/30 visual acuity or better as the criterion for normal visual acuity, eight eyes with letter visual acuities ranging from 20/42 to 20/138 would have been inaccurately found to be normal by using the Teller visual acuity cards alone. Grating visual acuity measurements tended to be better than letter visual acuity; and, in general, they did not worsen proportionately with poorer letter visual acuity.

WE EVALUATED the sensitivity of Teller visual acuity cards in identifying amblyopia in nonstrabismic, literate children with anisometropic amblyopia. Preferential viewing techniques have been used for infant and toddler visual acuity assessment for several years. Various techniques have been proposed and several reviews of these procedures have been reported.[1-4] Forced choice preferential looking and operant preferential looking typically require 15 to 45 minutes to derive a binocular visual acuity estimate. In 1985, McDonald and associates[5] introduced the visual acuity card procedure, which reduced testing time for binocular visual acuity assessment to three to five minutes. A commercial version of this practical infant visual acuity test is now available and is gaining acceptance. Few studies have been performed on visually abnormal patients who are sufficiently mature to provide both grating visual acuity and recognition visual acuity.[6-12] Therefore, the validity of the Teller visual acuity cards in detecting amblyopia is not established. Previous investigations[6-12] have not emphasized the patient group selected in our study; yet it is specifically this group that represents the greatest challenge. Strabismic children with amblyopia tend to obtain medical attention before anisometropic, nonstrabismic children with amblyopia, because the former usually have a cosmetic deformity, whereas the latter do not. Moreover, young children virtually never compare spontaneously the visual acuities of their eyes. Nonstrabismic children with amblyopia are without subjective complaints and appear objectively normal (no symptoms or visible signs). Anisometropic amblyopia tends to be detected at the time of the first preschool or school vision screening test.[13] In the United States, most children do not receive preschool vision tests.[14] Therefore, this population usually first receives medical attention at about 6 years of age. At this age, amblyopia therapy is difficult and usually not very effective.

Clinically significant amblyopia occurs in approximately 2% of the population.[15] The proportion caused by anisometropia is not known precisely. In some published amblyopia prevalence surveys, however, straight-eyed patients have constituted more than one half of the sample. Most patients presumably have anisometropic amblyopia.[16] If the visual acuity card procedure is to be used for screening purposes, it is important to know its effectiveness in this proportionately large group of amblyopic patients.

Patients and Methods

Children 8 years of age or older with aniso-metropic amblyopia were located from the computerized records of the Department of Ophthalmology at our institution. Families were paid to participate in the study, and each patient was offered a free, complete ocular examination. All spectacles worn were prescribed by physicians within one year. Many participating patients had been treated previously by occlusion therapy and all wore spectacles.

Both visual acuity tests were performed on both eyes of each patient at each testing session. The test given first, the eye tested first for each test, and, for the letter test, the chart used first were all determined by random assignments made previously by an original computer program. Consecutively numbered envelopes were used for assignment purposes.

One of us (D.L.M.) completed an instructional course in the visual acuity card procedure and had several months of practical experience in using the cards on infants and young children before participation in this study.

The visual acuity cards used were purchased from Vistech Consultants, Inc. (Dayton, Ohio). The step in spatial frequency between cards was one-half octave. The display apparatus consisted of a central, gray, cardboard screen with a rectangular opening against which the cards were held from behind. Two side panels are attached to the central panel. The luminance of the screen area was a uniform 10 candelas/m². The test distance was maintained at 55 cm from the patient's eyes to the peephole in the center of the visual acuity cards. The eye-to-card distance was measured repeatedly during each testing session by a tape measure and was kept constant by means of an overhead vertical panel, which tended to prevent forward head displacement. An assistant was needed to restrain the movements of a few of the younger children. The testing technique used was that described in the handbook provided by Vistech Consultants, Inc. Appropriate optical corrections were worn; the eye not being tested was covered by a commercially available adhesive eye patch. Children were asked to state the location of the stripes, either left or right. Eye movements were monitored continuously through the central peephole. Visual acuity scores were determined by integrating all available test data. The scores were converted from cycles/cm to cycles/degree and approximate

Snellen equivalents were derived from tables provided in the handbook by using the convention that 30 cycles/degree is numerically equivalent to 20/20 Snellen. Previously obtained visual acuity results were not available to the examiner (D.L.M.) at the time of repeat testing.

Two Bailey-Lovie-Ferris charts[17,18] were photographically reduced to 35 cm for viewing. Letter contrast was about 85%, similar to that of the gratings. Luminance was measured with a light meter and was kept the same as that of the gratings. A chin rest and forehead restraint device were used to assure constant measured test distances. Appropriate optical corrections were worn; an adhesive eye patch was used to occlude the nontested eye. Cover-uncover tests were performed at near fixation to assure absence of strabismus. Patients were asked to read all visible letters starting at the top of the chart. For some patients, the testing distance had to be decreased for the top letters to be seen. Each correct and incorrect response was recorded. Testing continued until four of five letters on a line were read incorrectly. Credit was given for all correct responses above that line by the method of interpolation described by Ferris and associates.[18] Different charts were used for right and left eyes. Previously obtained visual acuity data were not available to the examiner (D.S.F.) at the time of repeat testing.

All 32 patients tested were invited to return for repeat testing. Fifteen patients returned for the purpose of reliability evaluation. Testing procedures were carried out in the same sequence and by the same examiners on the second visit as on the first visit.

Results

Patients ranged in age from 8 to 17 years with a mean of 11 years. Twelve patients had hypermetropic anisometropia; 20 patients had myopic anisometropia. The degree of anisometropia in spherical equivalents ranged from 0.87 to 5.25 diopters for the hypermetropic eyes and from 0.50 to 12.25 diopters for the myopic eyes. The mean anisometropia for all patients was 4.59 diopters. The eye with the higher degree of anisometropia was in all cases the more poorly seeing eye by the letter test (Table).

Visual acuity results obtained by the two tests used were compared by using their LogMAR (logarithm of the minimal angle of resolution) equivalents. The results are shown in Figure 1.

TABLE
CLINICAL DATA OF VISUAL ACUITY MEASUREMENTS OF 32 PATIENTS

PATIENT NO., AGE (YRS)	EYE	REFRACTION	BAILEY-LOVIE-FERRIS VISUAL ACUITY CHARTS		TELLER VISUAL ACUITY CARDS	
			LOGMAR	20-FT. SNELLEN EQUIVALENT	LOGMAR	20-FT. SNELLEN EQUIVALENT
1, 10	R.E.	−0.50	−0.10	16	−0.10	16
	L.E.	−13.00 +0.50 × 90	0.90	159	0.50	63
2, 8	R.E.	−2.50 +0.75 × 180	0.22	33	−0.10	16
	L.E.	−15.50 +3.25 × 180	0.52	66	0.20	32
3, 16	R.E.	0.00	−0.06	17	−0.10	16
	L.E.	+4.75 +1.00 × 90	0.58	76	−0.10	16
	R.E.	0.00	−0.10	16	−0.10	16
	L.E.	+4.75 +1.00 × 90	0.74	110	0.08	24
4, 17	R.E.	−5.00 +1.50 × 90	0.06	23	−0.10	16
	L.E.	−9.50 +1.50 × 85	1.31	407	0.37	47
5, 14	R.E.	+2.00 +0.75 × 100	−0.10	16	−0.10	16
	L.E.	+4.00 +2.50 × 80	0.88	151	0.37	47
	R.E.	+2.00 +0.75 × 100	−0.14	14	−0.10	16
	L.E.	+4.00 +2.50 × 80	0.92	166	0.20	32
6, 14	R.E.	−9.50 +1.50 × 160	0.56	73	−0.10	16
	L.E.	−2.25	0.02	21	−0.10	16
7, 17	R.E.	−1.00 +0.25 × 90	0.00	20	−0.10	16
	L.E.	−8.00 +2.50 × 90	0.54	69	0.37	47
	R.E.	−1.00 +0.25 × 90	−0.02	19	−0.10	16
	L.E.	−8.00 +0.25 × 90	0.50	63	0.20	32
8, 17	R.E.	−10.75 +1.00 × 90	1.29	386	0.50	63
	L.E.	−2.25	0.06	23	0.08	24
9, 8	R.E.	−5.50	0.34	44	0.37	47
	L.E.	−10.50 +1.50 × 90	0.46	58	0.20	32
10, 9	R.E.	−18.50 +2.50 × 120	0.92	166	0.20	32
	L.E.	−10.50 +1.00 × 90	0.42	53	0.20	32
11, 8	R.E.	0.00	0.12	26	0.08	24
	L.E.	−2.00 +1.00 × 90	0.68	96	0.37	47
	R.E.	0.00	0.08	24	0.08	24
	L.E.	−2.00 +1.00 × 90	0.70	100	0.20	32
12, 11	R.E.	−6.00 +2.00 × 45	0.42	53	0.20	32
	L.E.	−2.50	0.00	20	0.08	24
	R.E.	−6.00 +2.00 × 45	0.36	46	0.08	24
	L.E.	−2.50	0.10	25	−0.10	16
13, 9	R.E.	0.00 +2.00 × 100	0.24	35	0.50	63
	L.E.	−0.75 +0.75 × 90	0.08	24	0.08	24
	R.E.	0.00 +2.00 × 100	0.28	38	0.20	32
	L.E.	−0.75 +0.75 × 90	0.10	25	−0.10	16
14, 8	R.E.	−2.75 +0.50 × 180	0.14	28	0.08	24
	L.E.	−7.75 +1.75 × 130	0.40	50	0.37	47
15, 8	R.E.	+0.75	0.22	33	−0.10	16
	L.E.	+4.00 +1.00 × 100	0.32	42	0.20	32
	R.E.	+0.75	0.12	26	−0.10	16
	L.E.	+4.00 +1.00 × 100	0.28	38	0.08	24
16, 11	R.E.	−7.25 +1.75 × 125	0.42	53	0.37	47
	L.E.	−1.50 +0.50 × 60	0.14	28	−0.10	16
	R.E.	−7.25 +1.75 × 125	0.46	58	0.37	47
	L.E.	−1.50 +0.50 × 60	0.04	22	0.08	24

TABLE *(Continued)*
CLINICAL DATA OF VISUAL ACUITY MEASUREMENTS OF 32 PATIENTS

| PATIENT NO., AGE (YRS)	EYE	REFRACTION	BAILEY-LOVIE-FERRIS VISUAL ACUITY CHARTS		TELLER VISUAL ACUITY CARDS	
			LOGMAR	20-FT. SNELLEN EQUIVALENT	LOGMAR	20-FT. SNELLEN EQUIVALENT
17, 11	R.E.	0.00	0.04	22	−0.10	16
	L.E.	+0.75 +0.25 × 90	0.84	138	0.08	24
	R.E.	0.00	−0.04	18	−0.10	16
	L.E.	+0.75 +0.25 × 90	0.92	166	−0.10	16
18, 9	R.E.	−4.50 +2.50 × 92	0.16	29	−0.10	16
	L.E.	−10.00 +4.00 × 85	0.74	110	0.37	47
19, 10	R.E.	−11.25 +0.75 × 120	0.26	36	0.20	32
	L.E.	−6.50 +1.75 × 90	0.12	26	0.20	32
	R.E.	−11.25 +0.75 × 120	0.30	40	0.20	32
	L.E.	−6.50 +1.75 × 90	0.02	21	−0.10	16
20, 12	R.E.	−1.25 +1.00 × 95	0.06	23	0.20	32
	L.E.	−12.50 +3.00 × 100	0.54	69	0.37	47
	R.E.	−1.25 +1.00 × 95	0.06	23	−0.10	16
	L.E.	−12.50 +3.00 × 100	0.40	50	0.50	63
21, 17	R.E.	0.00 +0.75 × 90	−0.04	18	−0.10	16
	L.E.	+3.00 +1.25 × 90	0.58	76	0.20	32
22, 12	R.E.	0.00 +0.50 × 90	0.06	23	−0.10	16
	L.E.	+3.50 +0.75 × 90	0.44	55	−0.10	16
	R.E.	0.00 +0.50 × 90	0.10	25	−0.10	16
	L.E.	+3.50 +0.75 × 90	0.44	55	0.08	24
23, 13	R.E.	−4.50 +2.50 × 75	0.22	33	0.20	32
	L.E.	−10.50 +5.00 × 110	0.64	87	−0.10	16
	R.E.	−4.50 +2.50 × 75	0.18	30	−0.10	16
	L.E.	−10.50 +5.00 × 110	0.68	96	0.08	24
24, 8	R.E.	−0.50	0.10	25	−0.10	16
	L.E.	−9.25 +2.00 × 180	0.60	80	0.08	24
25, 11	R.E.	+1.00 +1.50 × 90	0.32	42	0.08	24
	L.E.	0.00 +0.50 × 85	0.16	29	0.08	24
26, 11	R.E.	−1.75 +3.00 × 100	0.26	36	0.20	32
	L.E.	0.00 +0.50 × 90	0.02	21	−0.10	16
	R.E.	−1.75 +3.00 × 100	0.10	25	0.20	32
	L.E.	0.00 +0.50 × 90	−0.06	17	−0.10	16
27, 9	R.E.	+1.00	0.14	28	−0.10	16
	L.E.	+2.50	0.86	145	0.20	32
28, 9	R.E.	+1.00 +0.50 × 90	0.04	22	0.08	24
	L.E.	+4.50 +0.75 × 90	0.16	29	0.50	63
29, 8	R.E.	+3.50	0.34	44	0.20	32
	L.E.	0.00	0.02	21	−0.10	16
30, 15	R.E.	−2.75 +0.75 × 90	0.02	21	−0.10	16
	L.E.	−4.75 +1.50 × 80	0.10	25	−0.10	16
31, 8	R.E.	0.00 +0.25 × 180	0.00	20	−0.10	16
	L.E.	+1.75 +0.75 × 90	0.60	80	0.37	47
32, 8	R.E.	−8.00 +2.00 × 110	0.36	46	−0.10	16
	L.E.	−2.00 +1.00 × 95	0.26	36	−0.10	16
	R.E.	−8.00 +2.00 × 110	0.40	50	−0.10	16
	L.E.	−2.00 +1.00 × 95	0.30	40	0.20	32
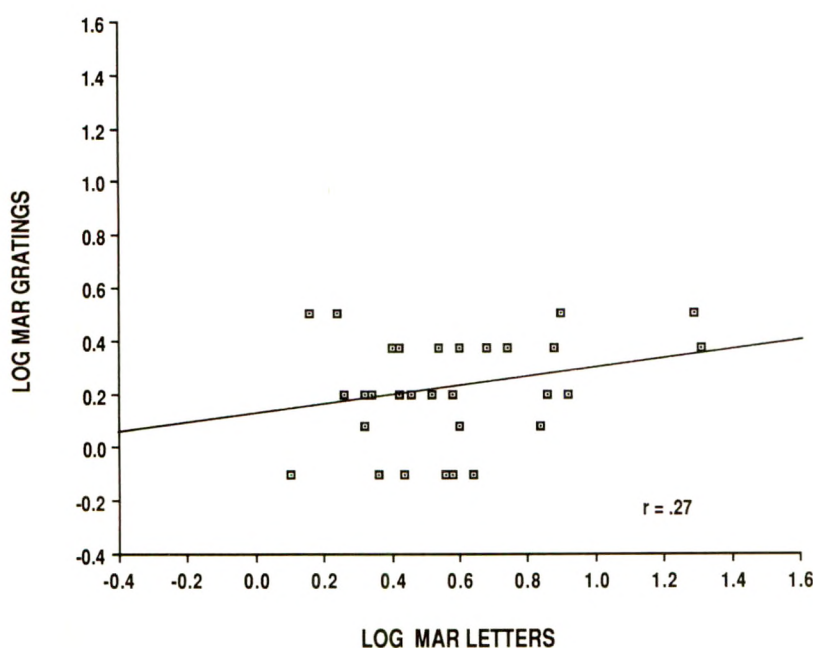
Fig. 1 (Friendly, Jaafar, and Morillo). Letter visual acuities (Log-MAR) compared with grating visual acuities (LogMAR) for amblyopic eyes. A line of best fit has been drawn through the scattergram.

In all but two cases, visual acuity scores were better by the Teller cards than by the Snellen letters. The slope of the regression line was 0.18, which indicates a tendency for the scores by the Teller cards not to worsen proportionately with poorer Snellen letter visual acuities. The product moment correlation coefficient was .27.

The interval between test and retest ranged from one to 22 weeks with a mean of 11 weeks. The results of intraobserver test-retest by Snellen letters are shown in Figure 2. The product moment correlation coefficient was .95. Test-retest results by Teller visual acuity cards are shown in Figure 3. The correlation coefficient was .68 by the Pearson product moment method and .80 by the Spearman rank method.

Discussion

Bailey-Lovie-Ferris charts were used in this study because they incorporate all but one of the recommendations of the Committee on Vision of the National Academy of Sciences–National Research Council.[19] The charts were reduced in size for near presentation to provide similar testing distances for both the resolution and recognition visual acuity tests.

LogMAR units were used in this study for both visual acuity tests, because barely noticea-

ble differences in visual acuity have the same numerical values throughout the LogMAR visual acuity scale.[20]

Of the 30 patients with amblyopia with letter visual acuities worse than 20/30, eight patients with visual acuity ranging from 20/42 to 20/138 by the letter test were found to have grating visual acuities of 20/30 or better. Using the 20/30 criterion (which seems reasonable since it is frequently used in visual acuity screening tests[21]) the sensitivity of the Teller cards was 22/30 or 73%. All patients wore appropriate corrections for both visual acuity tests. We did not test the amblyopic eyes of these patients without correction, as might occur in a screening session. Of the eight patients with false-negative results, four would have been expected to see as well with their amblyopic eyes without correction at the testing distance used.

Overall, performance was much better on the Teller test than on the letter recognition test. Only two patients had better visual acuities by the Snellen letters than by the visual acuity cards. Also, the differences between visual acuities tended to increase as recognition visual acuity worsened. Both of these findings have been previously reported.[8]

Test-retest correlation was good for the Snellen letters, but not as good for the Teller cards. More data points approached the line with a 45-degree slope representing perfect agreement between the two variables for the

Fig. 2 (Friendly, Jaafar, and Morillo). Letter visual acuities at first testing session (LogMAR) compared with letter visual acuities at second testing session (LogMAR). A line of best fit has been drawn through the scattergram.

Snellen letters than for the Teller cards, which indicates greater consistency as well as higher correlation by this method. Because of the discontinuous nature of the scale used for the Teller cards, the Spearman rank correlation coefficient may better represent the degree of association for this test-retest comparison.
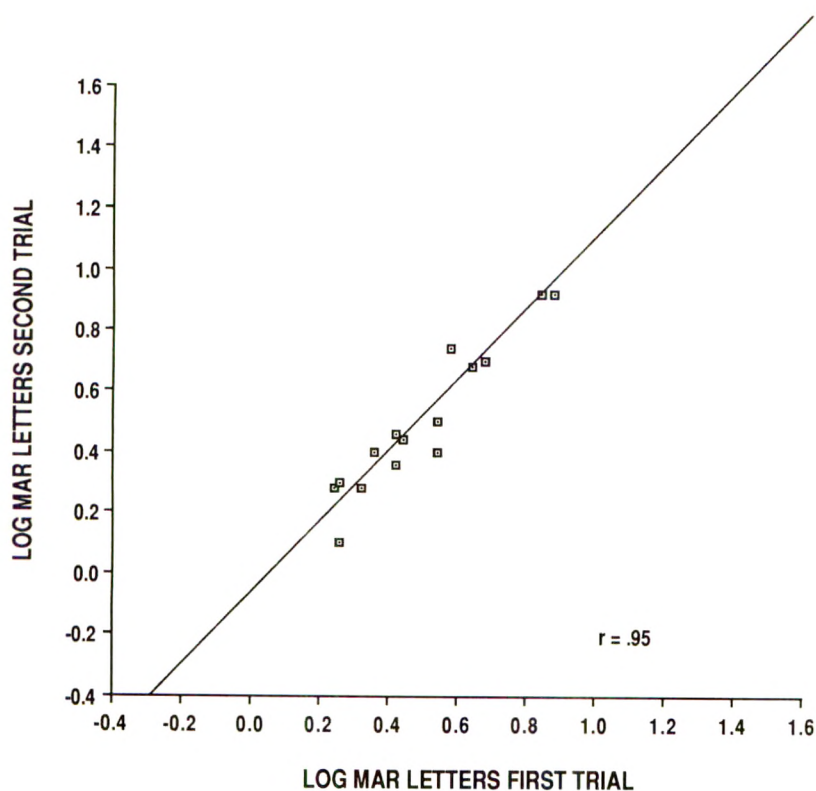
Most previous studies that have compared
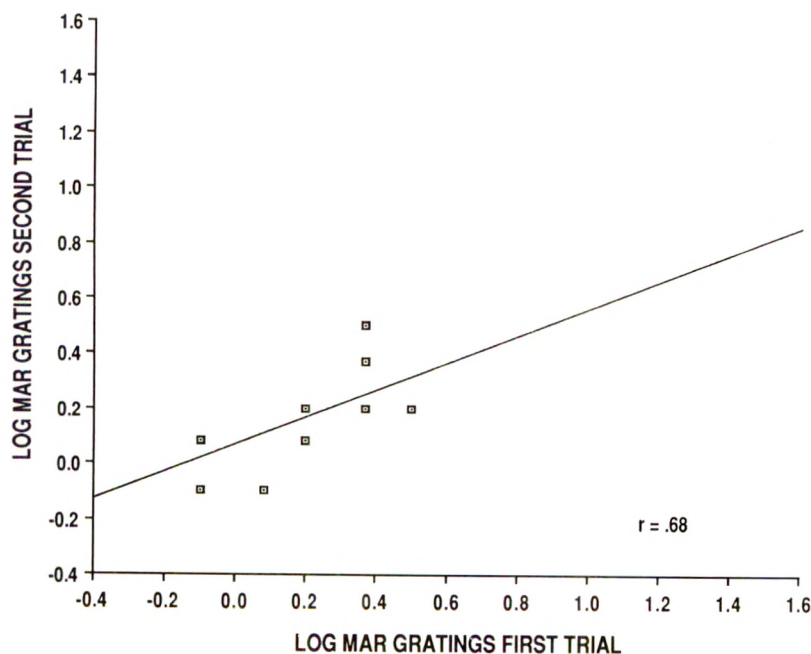

Fig. 3 (Friendly, Jaafar, and Morillo). Grating visual acuities at first testing session (LogMAR) compared with grating visual acuities at second testing session (LogMAR). A line of best fit has been drawn through the scattergram.

grating and recognition visual acuity tests of amblyopic eyes have found better visual acuity scores by the grating method than by the recognition method.[6-11] However, in one carefully documented report, the two measures correlated reasonably well.[12] The authors of this report used nonstandard presentation and scoring methods and did not use Teller visual acuity cards. Possible reasons for the disparity between the two visual acuity measurements for patients with anisometropic amblyopia have been reported in detail by Mayer, Fulton, and Rodier.[8] These authors mentioned differences in testing methodology, spurious resolution of repetitive patterns, nonlinearities in neural processing, and dissimilarities in object field size as potentially contributing factors. Other reported possible contributing factors include contrast sensitivity differences between the gratings and letters based on stimulus size differences[10] and artifacts originating from the edges of the gratings.[22]

Our study does not address directly the potential usefulness of Teller visual acuity cards for amblyopia screening of infants, the population for which they were designed. However, the reliability and validity of Teller visual acuity cards as an amblyopia screening test for such patients may be less than optimum. Based on the results of this study, it would appear that Teller visual acuity card scores for children with anisometropic amblyopia need to be interpreted cautiously.

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Functional Eyelid Pulling in Children

Robert A. Catalano, M.D., Mary Gina Trevisani, M.D., and John W. Simon, M.D.

Five children (three girls and two boys, aged 3½ to 9½ years) were referred by their pediatricians for evaluation of intermittent pulling on their eyelids. All the children were free of systemic disease. One child wore spectacles for accommodative esotropia but no child had evidence of an acute ocular disorder. The duration of symptoms before examination ranged from one to 13 months. None of the parents were able to identify temporally related stressful events. Reassurance alone was given to both parents and children; eyelid pulling resolved in all cases within two weeks. In only the youngest patient did eyelid pulling recur and no child developed other symptoms during a follow-up of six to 15 months. Following resolution, parents believed their children pulled on the eyelids to gain attention or because their eyes were initially irritated and they then developed a "bad habit." Children said they did it to "look funny" or because their "eyes were not opening enough."

CHILDREN AND ADULTS may pull on their eyelids to relieve ocular irritation secondary to misdirected eyelashes, a foreign body, or an inflammatory disorder of the eyelid. Occasionally, the eyelids may be pulled to simulate a stenopeic slit to reduce an uncorrected refractive error, or to relieve diplopia related to an uncorrected strabismic disorder. Eyelid pulling, unrelated to an organic disorder, is an unusual clinical problem.

We studied the course of children who pulled their eyelids in the absence of an underlying ocular or systemic disease. Associated stresses, the parents' and child's belief regarding causative factors, and the parents' belief regarding factors responsible for resolution were examined.

Patients and Methods

All children seen during 1989 at the Pediatric Ophthalmology Service of Albany Medical College with the primary symptom of pulling on their eyelids were identified. Five children without associated acute ocular or systemic disorder were entered in the study. One child with allergic conjunctivitis and a second child with an uncorrected refractive error were excluded. Every child had been referred by a pediatrician for evaluation of this symptom.

Ocular and systemic histories were obtained from the parent accompanying the child. Complete ocular examination including visual acuity testing with projected Snellen letters or Allen pictures, refraction, biomicroscopy, and indirect ophthalmoscopy was performed on all children. Two to three months after the initial examination every child was reexamined or their parents interviewed by telephone to determine the course of symptoms and the emergence of subsequent diagnoses. All parents were again interviewed, six to 15 months after initial examination, for extended follow-up.

Results

The ages of the children at examination ranged from 3½ to 9½ years (mean, 7 years). There were three girls and two boys.

Typically, children pulled both lower eyelids downward or both eyelids outward from the

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Fig. 1 (Catalano, Trevisani, and Simon). Eyelid pulling in a 3½-year-old girl.

Fig. 2 (Catalano, Trevisani, and Simon). Eyelid pulling in a 7-year-old boy.

lateral canthus (Figs. 1 through 5). They did this from 10% to 50% of their waking hours, particularly when sitting with their gaze fixed, watching television (four children) or reading (one child). Only one child had another symptom of occasionally seeing colored, floating spots. No child had associated headaches, and no child believed that they saw better when pulling the eyelids. Only two children complained of ocular irritation only when directly asked. No history of school- or family-related stresses could be elicited. Three children could readily name friends who pulled their eyelids in a similar manner.

Visual acuity measured 20/20 in both eyes, using projected Snellen letters in the four oldest children, and 20/30 using projected Allen pictures in the youngest child. Visual acuities were obtained without correction except for the child with accommodative esotropia. With the exception of this child no child had any other ocular disorder. Every child was orthophoric at both distant and near fixation. Except for the child with accommodative esotropia, this was measured without correction.

The duration of symptoms at the time of examination ranged from one to 13 months.

The only treatment offered was reassurance and follow-up. The duration of symptoms after examination ranged from immediate resolution to two weeks. During follow-up of six to 15 months only the youngest child began to pull her eyelids again. In this child eyelid pulling had stopped completely for two weeks, two weeks after her examination, but slowly began to recur. Fifteen months later she still pulled her eyelids when watching television or movies. No child developed other symptoms.

Following resolution, parents believed their children developed the behavior because they wanted attention (three children), or because their eyes were initially irritated and they developed a "bad habit" (two children). The children stated that they did this to "look funny" or they "liked to do it" (three children), or because "their eyes were not opening enough" (two children). Two parents believed the physician's reassurance was responsible for resolution of symptoms. Two parents believed intimidation, including suggesting to their child that the eyelids would stay stretched, led to resolution.

Discussion

Two medically benign and self-limited visual disorders in childhood, functional visual loss[1]

Fig. 3 (Catalano, Trevisani, and Simon). Eyelid pulling in a 9½-year-old boy.

Fig. 4 (Catalano, Trevisani, and Simon). Eyelid pulling in a 7-year-old girl.

Fig. 5 (Catalano, Trevisani, and Simon). Eyelid pulling in an 8½-year-old girl.

and functional blinking,[2] have been described. In these conditions reassurance alone usually leads to a rapid resolution of symptoms; once this occurs recurrence of symptoms is rare. Functional visual loss is often associated with conflict related to school or family.[1] The principal secondary gain in functional blinking appears to be increased attention from the caretaker.[2]

Functional eyelid pulling is similar in its rapid resolution following reassurance alone and in its tendency not to recur. It differs from functional visual loss by occurring in the absence of a temporally related and recognizable stressful event. Our results suggest that the attention gained from peers, parents, and teachers may be reinforcing, similar to the experience of children with functional blinking. The grotesque appearance and concern about a possible disorder often provoke an ophthalmic examination, thereby increasing the attention received. In some instances the action may simply be a habit formed in response to an initial ocular irritation.

Similar to functional blinking, but unlike functional visual loss, eyelid pulling occurs in a younger age group and there does not appear to be a predominance of females. The propensity of functional visual loss to occur in late childhood has been attributed to the physical and emotional stresses of early adolescence.[3] Conflict related to school or family is less apparent in the other two disorders.

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OPHTHALMIC MINIATURE

B. is so vulnerable when it comes to his appearance, especially his eyes. His eyes are devastating, everyone comments on his penetrating gaze–*but I am the only one who understands how he suffers. Astigmatism!* What a cruel trick of fate that someone who sees through the sham in all people should be cursed with astigmatic vision.

Susan Brownmiller, *Waverly Place*
New York, Grove Press, 1989, p. 153

EDITORIAL

Kass Heads Abstract Section

Frank W. Newell

With this issue Michael A. Kass, M.D., professor of Ophthalmology at Washington University, assumes editorial responsibility for the abstract section of The Journal. He brings to this post an exceptional awareness of the current aspects of every phase of ophthalmology combined with a searching and discerning mind. He has been an associate editor of The Journal since 1986 and has participated fully in the management of The Journal editorial affairs.

Together with Dunbar Hoskins, he produced a fully revised 6th edition of Becker and Shaffer's Diagnosis and Therapy of the Glaucomas. Additionally, he chaired the Glaucoma Section for Research in Vision and Ophthalmology, and Section VIII of the Basic and Clinical Science Course of the American Academy of Ophthalmology. He thus continues the traditional strength of the abstract section.

The abstract section is the descendent of the Ophthalmic Year Book first written entirely by Dr. Jackson in 1904 that provided a series of essays that encompassed some 800 references. Subsequently, Jackson enlisted authorities to prepare various reviews based on articles published the previous year.

The Year Book was issued monthly when the current series of The American Journal of Ophthalmology appeared in 1918. In 1922, Dr. William H. Crisp, Jackson's Denver colleague assumed editorship of the Year Book while Jackson continued as editor of The Journal. In addition to the Year Book, The Journal published a list of current articles each month under the heading of Current Literature. These lists included nearly every available medical journal together with a number of those dealing with general medicine. The lists were sent to the different authorities responsible for different sections of the Year Book to assist them in their articles. Crisp estimated that often less than 50% of the listed articles were available to

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the writers of the various sections and that most authors were not familiar with many of the languages. (Dr. Crisp had an innate sense of style in English and a command of seven foreign languages.)

The Year Book and Current Literature Listing discontinued publication in 1927 for lack of financial support. An extensive abstract section appeared in THE JOURNAL. Lawrence T. Post of St. Louis became editor of THE JOURNAL July 1, 1931. William Crisp then joined Jackson as consulting editor and was named editor of the abstract section. Until that time the abstract section had not listed an editor, although Crisp was recognized as editing both THE JOURNAL and the abstract section. Crisp continued to edit the abstract section until January 1946 when F. Herbert Haessler of Milwaukee was appointed. In the announcement of Haessler's appointment, Crisp mentioned that he devoted a substantial share of his time for 35 years to the Year Book, the general editorship of THE JOURNAL, and the supervision of the abstract department. Dr. Haessler had served as a collaborator on the Year Book and then for many years assisted in the preparation of abstracts for THE JOURNAL

(Am. J. Ophthalmol. 29:102, 1946). Haessler edited the abstract section until 1963. In February 1964, David Shoch succeeded him as editor.

With the publication of Ophthalmic Literature and the Excerpta Medica abstract service, and more recently computerized information services, the need for complete or nearly complete abstracts has diminished. Additionally, an increasing number of ophthalmologists specialize in a particular topic and most ophthalmologists no longer feel compelled to be familiar with the world's ophthalmic literature. Under Dr. Shoch the many loyal collaborators who for many years had prepared abstracts of articles gradually decreased in number and with it the abstract section.

Dr. Kass plans a number of changes in the abstract section that will be evident in this and the succeeding issues. Abstracts will be identified by topics and not by the journal in which they appeared. A broader survey is planned with abstracts being derived from articles dealing with ethics, economics, and the whole spectrum of ophthalmology. The name and address of the individual to whom to write for reprints will be included at the end of each abstract.

LETTERS TO THE JOURNAL

Light Deprivation and Retinitis Pigmentosa

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Damage of photoreceptors by hereditary degeneration[1,2] or vitamin A deficiency[3] has been reported to be accelerated by light exposure in the rat. Thus, light deprivation has been considered to be of possible therapeutic benefit to patients with retinitis pigmentosa. In 1980, Berson[4] examined two patients with retinitis pigmentosa of different hereditary modes. Each patient wore an opaque scleral contact lens[5] on one eye for approximately six to eight hours per day during a five-year period. However, light deprivation did not modify the rates of progression of this disease.

We examined a 37-year-old man at our institution in 1970 because of night blindness in the left eye. Thirty years earlier, the patient had a trauma to the right eye, which resulted in poor visual acuity. The right eye showed a scar in the superior cornea. The pupil was occluded by the iris. Under the iris, we noted a thick, white membrane through a pinhole pupil. Visual acuity was R.E.: hand motions.

In the left eye, visual acuity was 20/16. The visual field in the left eye demonstrated a substantial constriction to the 5-degree isopter with a I_4 test object and full fields with a V_4 white test on Goldmann perimetry. Dark adaptation thresholds remained at 1.7 log units above normal. The fundus showed findings typically seen in relatively early retinitis pigmentosa, including attenuation of retinal vessels and bone spicule pigmentation in the midperipheral fundus.

Electroretinograms were recorded with single white stimuli of changing intensities (Fig. 1). The response was recordable in both eyes,
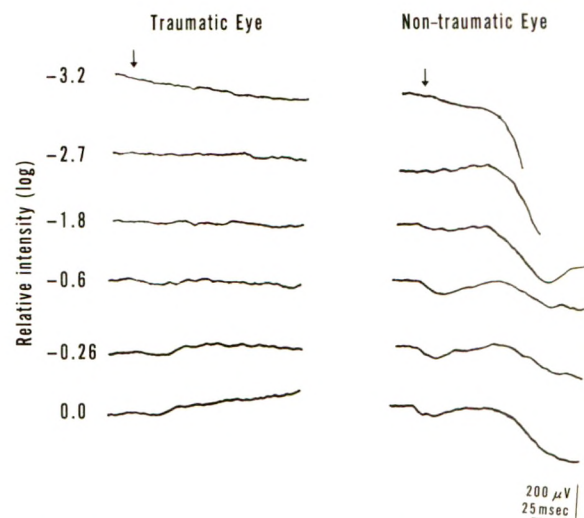

Fig. 1 (Miyake and associates). Electroretinograms recorded with single white stimuli of changing intensities. Numbers to the left indicate stimulus intensities in log units. The maximum intensity (0.0) is 80 J. Arrows indicate a stimulus onset. This recording was done in 1970, 30 years after trauma.

Fig. 2 (Miyake and associates). Postoperative findings of the anterior segment in the right eye.

but only when the stimulus was intense. Retinitis pigmentosa was diagnosed. There was no family history of the disease.

The retinitis pigmentosa gradually progressed and in 1982, visual acuity was R.E.: light perception and L.E.: 20/30. An annular maculopathy was observed in the left fundus. We opened the closed pupil of the right eye by using a vitrectomy instrument to remove the iris of the pupillary zone and the thick membrane behind the iris through the pars plana. The postoperative finding is shown in Figure 2. Before and after the operation, we measured the subjective light threshold of the right eye by changing intensities of full-field stimuli. The postoperative light threshold was 1.2 log units below the preoperative threshold. This result indicates that a filter density of 1.2 log units was removed by surgery. The right eye had been covered with a 1.2-log unit density filter for 42 years.

The right and the left fundi were compared in terms of distribution of bone spicule pigmentation, degree of retinal vessel attenuation, color of the optic disk, and macular status. Little difference in fundus appearance was detected. There was no sign that the traumatic damage in the right eye involved the posterior segment. The preoperative visual acuity of light perception increased to hand motions postoperatively, but remained far lower than the visual acuity in the left eye (20/30). The lower visual acuity was most likely caused by stimulus deprivation amblyopia, since the right eye had been deprived of stimulus for 42 years, and the ophthalmoscopic macular findings were essentially the same in both eyes.

Full-field electroretinography was performed postoperatively. Cone, rod, 30-Hz flicker, and single bright flash electroretinograms were no longer recordable in either eye. We again compared the electroretinograms obtained for the right and left eyes in 1970 (Fig. 1), taking into account the 1.2-log unit neutral density filter created by trauma in the right eye. The electroretinograms recorded with comparable stimulus intensities in the traumatized eye never exceeded the response in the untraumatized eye. Light deprivation, even for more than 40 years, did not make the progression of retinitis pigmentosa slower in our patient.

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Familial Anterior Ischemic Optic Neuropathy and Papillophlebitis

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Anterior ischemic optic neuropathy is a common cause of significant visual loss in adults.[1] Papillophlebitis is an uncommon cause of mild

visual impairment in young adults.[2] We studied bilateral anterior ischemic optic neuropathy in twin sisters and unilateral papillophlebitis in a third sister.

A 41-year-old woman was examined because of pain and mild visual impairment in her right eye for one month. Visual acuity was 20/20 in both eyes. The anterior segments and pupillary reaction were normal. In the right fundus an elevated hyperemic optic disk with blurred margins, edema of the surrounding nerve fiber layer, and marked venous engorgement with perivenous hemorrhages were visible (Fig. 1). Color vision, light brightness, and visual fields were normal as were results of general physical and neurologic examination, serologic, and hematologic studies. Ultrasound Doppler of the carotid arteries and computed tomography of the orbits did not demonstrate any relevant abnormality. A diagnosis of papillophlebitis in the right eye was made, and aspirin treatment was recommended. The clinical picture returned to normal within six months.

The patient had two brothers and five sisters, two of whom were 49-year-old identical twins with a history of bilateral nonarteritic anterior ischemic optic neuropathy.

We examined all the family members but found no detectable systemic, vascular, hematologic, or ophthalmologic abnormalities. In
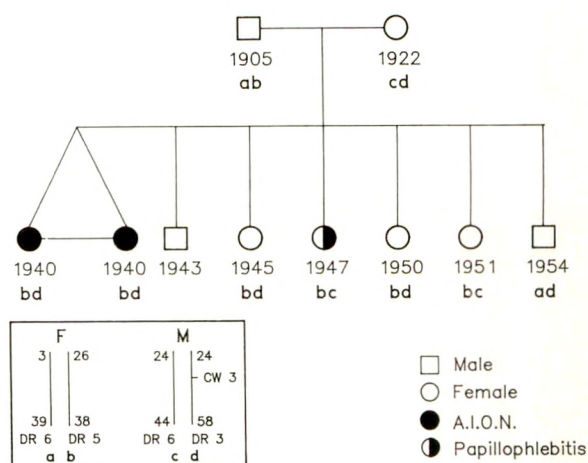
Fig. 2 (Deutsch and associates). Familial pedigree, dates of birth, and HLA typing distribution. Inset, Parents' haplotypes are represented by a, b (F, father); and c, d (M, mother). One brother was unavailable for blood tests. A.I.O.N. indicates anterior ischemic optic neuropathy.

order to define a certain genetic pattern common to the affected sisters, HLA typing was performed (Fig. 2). The affected twins had an identical pattern that was also found in two other younger, unaffected sisters. The sister with papillophlebitis had a different pattern that was shared by another unaffected sister.

Berggren, Thorburn, and Fodstad[3] described the rare occurrence of anterior ischemic optic neuropathy in two members of the same family. A man had five children from his first marriage who were normal. He remarried, and three of seven children from the second marriage were affected by anterior ischemic optic neuropathy, two bilaterally and one unilaterally. We believe the occurrence of ischemic optic neuropathy in two members of the same family, and specifically in identical twins, is not incidental, but related to a common genetic pattern. Such affected individuals are susceptible to vascular damage, which in this case was manifest as anterior ischemic optic neuropathy. Probably environmental factors also play a role. In the case reported by Berggren, Thorburn, and Fodstad,[3] the children from the first marriage were all normal. It was only after the second marriage that a genetic pattern was created, which together with environmental factors led to ischemic optic neuropathy in three of seven siblings.

We postulate that the episode of papillophlebitis in the third sister in our case was related to a somewhat different genetic pattern. Although
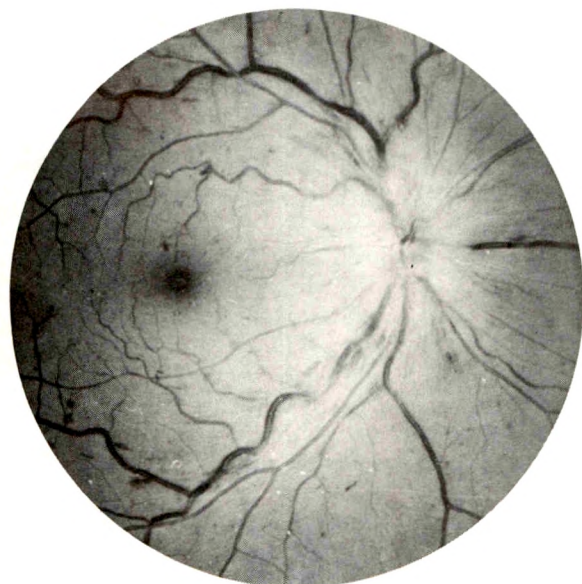

Fig. 1 (Deutsch and associates). Optic disk edema, venous engorgement, round and flame-shaped hemorrhages in the fundus of the right eye of a 41-year-old woman.

she shared some characteristics with those of the sisters affected by ischemic optic neuropathy the differences made her susceptible to vascular damage of a less severe degree. Probably because she was eight years younger, with better perfusion, was beneficial.

We regard all the family members as sharing an increased risk of vascular impairment, and they should be followed up regularly.

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Near Syncope and Chest Tightness After Administration of Apraclonidine Before Argon Laser Iridotomy

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Apraclonidine hydrochloride is an alpha-2 agonist currently approved for topical administration for prophylaxis against intraocular pressure increase after argon laser trabeculoplasty and iridotomy.[1] The drug has been used increasingly in Nd:YAG laser posterior capsulotomy procedures and has no major reported cardiovascular side effects. We treated a patient with chest tightness, loss of radial pulse, and near syncope after treatment with topical apraclonidine hydrochloride one hour before planned argon laser iridotomy.

A 67-year-old white woman with no history of heart disease, arrhythmia, or syncope had chronic angle-closure glaucoma. She had a his-

tory of systemic hypertension, diabetes, and renal stones. Her regular medications were 72 units of insulin isophane, 80 mg of furosemide, and 50 mg of metoprolol three times daily. She had no medical allergies. The patient received one drop of 1% apraclonidine hydrochloride in the right eye one hour before planned argon laser iridotomy and was seated in a waiting area.

Approximately ten minutes after the instillation of the drug, the patient complained of chest tightness. Her radial pulse was checked and found to be strong and regular. Within one to two minutes, the pulse had become undetectable, and the patient complained of feeling faint. She was immediately placed on a stretcher and taken to an adjacent surgical recovery area. An intravenous line was opened, and a cardiac monitor was used. The first blood pressure measurement, taken approximately five minutes after the initial complaint, was 170/80 mm Hg. At this time her pulse rate was 70 beats per minute and regular, and her blood glucose level was 180 mg/dl. An electrocardiogram showed a sinus rhythm with no acute changes. The patient remained stable and was later discharged. When interviewed, she denied that she had felt particularly anxious before the procedure and explained that her symptoms had a sudden and unexpected onset. A few days later the patient underwent successful argon laser iridotomy without the use of apraclonidine hydrochloride and had no difficulty.

The beneficial effects of apraclonidine hydrochloride as a prophylactic agent for acute intraocular pressure increase caused by argon laser iridotomy, trabeculoplasty, and Nd:YAG posterior capsulotomy have been well established.[1] A study of 21 patients (28 eyes) undergoing argon laser iridotomy and treated prophylactically with apraclonidine hydrochloride showed no eyes with intraocular pressure increases greater than 6 mm Hg, whereas 43% of placebo-treated eyes had intraocular pressure increases of 10 mm Hg or more.[2] The same study reported a vasovagal reaction attributed to anxiety, but the sample was too small to permit conclusions regarding cardiovascular effects.

The blood-brain barrier is less permeable to apraclonidine hydrochloride than to clonidine,[1] therefore diminishing the potential for systemic side effects caused by the former drug. In rats, topical apraclonidine has one tenth the hypotensive effects of clonidine.[3] In healthy human

volunteers not taking any medications, the systolic blood pressure decreased 2.8% from baseline and the diastolic blood pressure decreased 6% to 13% after 15 days of treatment with topical 1% apraclonidine hydrochloride twice daily.[4] It was also noted that 10% of the subjects had a diastolic blood pressure decrease of more than 20% at Day 8 and 26% at Day 15. The pulse rate changes ranged from an increase of 44% to a decrease of 42%. When compared to clonidine these effects are nevertheless negligible.[3]

No studies are currently available on the acute or chronic cardiovascular effects of apraclonidine hydrochloride in the elderly, hypertensive, diabetic population with documented or undocumented organic heart disease, and who are being treated with multiple systemic medications. Many such patients undergo procedures for which apraclonidine hydrochloride prophylaxis is being used. It is therefore wise to monitor blood pressure, heart rate, and patient complaints in selected cases, after the administration of apraclonidine hydrochloride. Knowledge of systemic medications the patient is taking may be of special value.

Further investigation of the cardiovascular effects of apraclonidine hydrochloride in the elderly, as well as studies to determine the effectiveness of solutions of lower concentration in the prophylaxis against intraocular pressure increase in laser surgery, are still needed to assure the safety of this useful pharmacologic agent.

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Corneal Endothelial Changes in Ocular Hypertensive Individuals After Long-term Unilateral Treatment With Timolol

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There has been some controversy about whether topical administration of timolol damages the corneal endothelium. Alanko and Airaksinen[1] found that two weeks of timolol treatment had no adverse effect on the corneal endothelium. In contrast, Brubaker, Nagataki, and Bourne[2] found a mean 6% reduction in corneal endothelial cell density after one year of timolol therapy in patients with glaucoma. They questioned whether the adverse corneal changes were caused by the preservative, benzalkonium chloride, or by timolol itself.

Between 1981 and 1988 we studied the effect of unilateral timolol therapy on the development of glaucomatous damage in patients with ocular hypertension.[3] One eye of each patient was allocated to therapy with either 0.25% or 0.5% timolol twice daily. The fellow eye received a placebo (timolol vehicle) twice daily. Both solutions contained benzalkonium chloride 0.01% as the preservative agent.

Thirty-five of the 62 patients were followed up for a minimum of 60 months. Twelve of these 35 patients were selected randomly and underwent specular microscopy and corneal pachymetry at the conclusion of the trial. The group consisted of seven men and five women with a mean age of 62 ± 8 years (range, 48 to 79 years). The mean treatment period was 84 ± 6 months. Endothelial cell structure was assessed by a masked observer (L.A.G.) from enlarged photographs of the central cornea.

The mean corneal thickness was 0.51 ± 0.08 mm for the eyes treated with timolol and 0.51 ± 0.09 mm for the placebo-treated eyes. The mean corneal endothelial cell density was 2,341 ± 364 cells/mm^2 in the timolol-treated eyes and 2369 ± 321 cells/mm^2 in the placebo-treated eyes. Neither of these differences was statistically significant (P = .918 and P = .729

respectively). Eleven eyes had subtle pleomorphism and eight eyes had mild to moderate polymegathism. However, these changes occurred with equal frequency in timolol-treated and placebo-treated eyes.

Corneal endothelial cell density has been shown to decrease with age. The cell densities obtained in our patients are consistent with the values predicted by the regression line reported by Bourne and Kaufman.[4] The cell counts we noted, however, are somewhat higher than that previously reported by Korey and associates.[5] Although baseline measurements of cell density were not available, we believe that the lack of significant differences between the two groups for all variables tested indicates that long-term timolol use has little effect on the corneal endothelium. We emphasize, however, that by using a sample size of 12 patients we would not detect an increased susceptibility to timolol in a small subset of the ocular hypertensive population.

It is possible that unilateral administration of timolol had a bilateral and equal toxic effect on the corneal endothelium. Timolol has been shown to cause bilateral intraocular pressure reductions after unilateral instillation. However, unilateral administration would yield a much higher concentration of timolol in a contralateral vascular tissue, such as the ciliary body, than in a contralateral nonvascular tissue, such as the corneal endothelium. Furthermore, unilateral administration would produce a far higher concentration in the ipsilateral cornea than in the contralateral cornea. If timolol were toxic to the corneal endothelium, one would expect a greater effect in the eye with the higher drug concentration.

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Use of the Argon Laser to Avoid Complications From Incomplete Removal of Corneal Sutures With Deeply Buried Knots

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Incomplete removal of corneal sutures can cause complications such as corneal vascularization and infectious keratitis[1] (Fig. 1). Retained sutures occur more commonly when knots are buried well below the stromal surface. When such knots resist removal, the common practice is to place the exposed suture under tension and cut it flush to the surface so that the
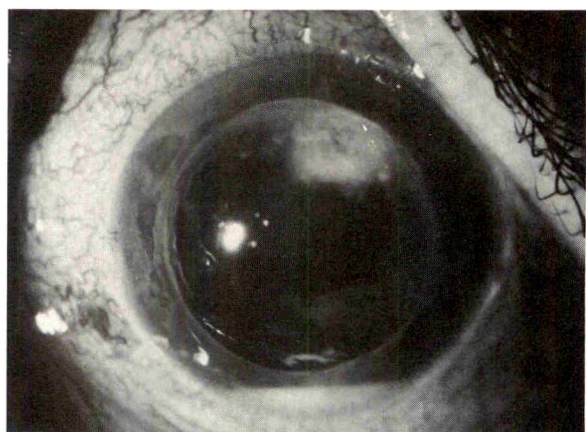

Fig. 1 (Bourne and Maguire). Hypopyon ulcer that resulted from retained nylon suture with buried knot that gradually extruded through the epithelial surface at the one o'clock meridian.
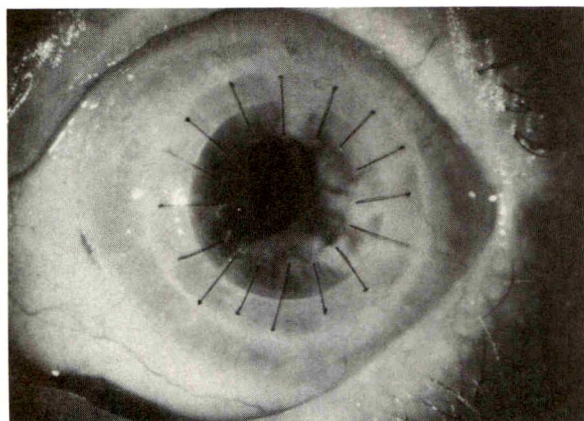
Fig. 2 (Bourne and Maguire). Penetrating keratoplasty with unburied compact knots pulled tight against recipient Bowman's layer. The epithelium is intact over the knots, and there is no reaction around them. The 6-mm graft is placed within a previously failed graft in this vascularized cornea.

suture tip will retract a safe distance below Bowman's layer. Unfortunately, this retraction is not guaranteed.

For corneal sutures with large, deeply buried knots, we suggest an alternative approach for removal that is more effective at placing the remaining suture tip well below the corneal surface. We find it convenient to sever the suture on each side of the knot with the argon laser. Laser settings of 300 to 500 mW, 50-μm spot size, and 0.2-second duration are adequate. If the laser beam is properly focused, one application suffices to cut the suture at the appropriate point. Jeweler's forceps retrieve the entire suture except the knot.

Although we find this technique useful, the best method of avoiding complications from retained sutures is to reduce knot size and place knots on or just below Bowman's layer. If the knots are tied flat and tight with one triple and two single throws, the ends cut flush with the knot, and the knots pulled tight against Bowman's layer, they will easily be covered by epithelium and cause no irritation, inflammation, or vascularization.[2] By using these techniques, we rarely find it necessary to bury suture knots in the cornea (Fig. 2). If the compactness of a particular knot or the shortness of its cut ends is not optimum, the surgeon can pull the knot into Bowman's layer, just beneath the epithelial surface, from where it can be more easily removed later.

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Corneal and Iris Burns With the Laser Indirect Ophthalmoscope

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We observed superficial corneal and iris burns complicating laser indirect ophthalmoscope treatment[1] of retinal disease in five patients. Four cases involved vitrectomy, including two for vitreous hemorrhage and retinal detachment from posterior retinal breaks. The other two cases involved performing panretinal photocoagulation in two patients with diabetic retinopathy and one with a central vein occlusion. One of the patients with diabetic retinopathy was treated in the outpatient laser room. During treatment good retinal laser uptake was initially observed, but then retinal absorption became sporadic. Small puffs of smoke were observed rising from the eye and there was a burning odor. Immediate inspection of the cornea disclosed clusters of small, white opacities with less than or equal to 10% thickness corneal excavation (Fig. 1, left). In two cases copious irrigation and removal of the corneal epithelium allowed continuation of treatment. In each case, the corneal opacities were in the peripheral cornea since they occurred during peripheral retinal laser treatment. The epithelial defects resolved with a routine postoperative regimen of semipressure patching and cycloplegic, antibiotic, and corticosteroid eyedrops. Anterior
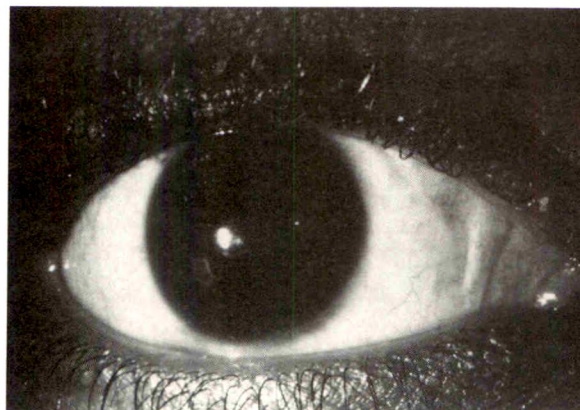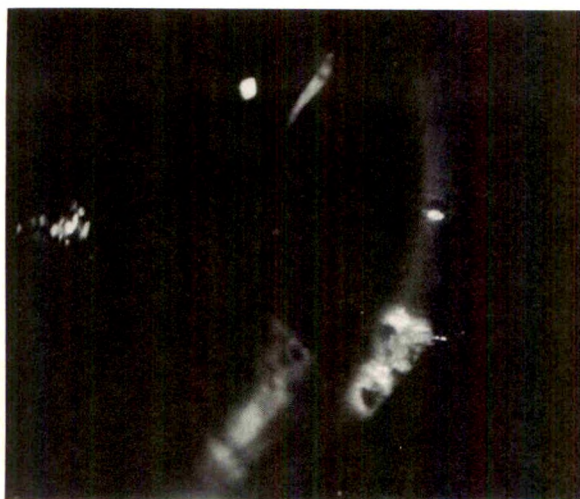
Fig. 1 (Irvine, Smiddy, and Nicholson). Left, Appearance of cornea on the first postoperative day. Clusters of corneal excavation are apparent inferonasally. Right, Appearance of cornea two months postoperatively in another patient. Corneal epithelialization is complete, and the patient has attained 20/50 visual acuity. Anterior stromal opacities persist.

corneal stromal opacities, though asymptomatic, however, persisted in two cases (Fig. 1, right). In Case 5 the iris burns were associated with a localized nonprogressive lens opacity (Fig. 2). No symptoms were attributable to these corneal opacities.

Corneal epithelial defects are a well known complication of vitrectomy especially in diabetic patients.[2] Edematous corneal epithelium that obscures the surgeon's view during vitreoretinal surgery may be removed intentionally to facilitate visualization and completion of surgery. Usually the epithelial defect heals rapidly without complication, but it may predispose the eye to corneal infection or erosions, which require prolonged treatment. A diffuse, deep stromal haze occasionally occurring after xenon arc photocoagulation attributed to heating of aqueous humor by extensive iris uptake has been reported.[3,4] This deep stromal haze was distinctly different from the focal superficial burns seen in our patients. In our cases the corneal uptake was associated with the latter stages of treatment and may have been attributable to energy absorption by the edematous corneal epithelium or undesired absorption caused by laser light scattering at the corneal surface.

Iris burns have been recognized as a frequent complication of xenon arc photocoagulation and are sometimes followed by a mild, corticosteroid-responsive iridocyclitis.[5] Focal anterior

subcapsular lens opacities and posterior synechiae were also seen in phakic eyes adjacent to iris burns, but these were nonprogressive and did not decrease vision. We have also seen eyelashes singe, burn, and melt when struck by the laser indirect ophthalmoscope beam.

The vitreoretinal surgeon should be aware of these potential complications to avoid or minimize the potential for postoperative morbidity. Optimizing the aiming beam focus and irrigating or denuding edematous corneal epithelium during treatment is recommended.

Fig. 2 (Irvine, Smiddy, and Nicholson). Iris burns at nasal pupillary margin with underlying anterior subcapsular lens opacities 24 hours postoperatively.

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A Simple Method for Assessing Laser Photocoagulation Coverage of Choroidal Neovascular Membranes

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The Macular Photocoagulation Study demonstrated the effectiveness of laser treatment for choroidal neovascular membranes associated with age-related macular degeneration,[1] ocular histoplasmosis,[2] and idiopathic causes.[3] Failure to cover the entire membrane was associated with a higher persistence rate for patients with choroidal neovascular membranes associated with ocular histoplasmosis 1 to 199 μm from the center of the foveal avascular zone.[4] To help identify untreated portions of a membrane at the time of photocoagulation thereby reducing the chance of persistence, members of the Macular Photocoagulation Study reported their method of assessing laser treatment of choroidal neovascular membranes.[5] Their technique involved making a composite drawing, which compared the extent of the neovascular membrane to the area of heavy laser photocoagulation treatment. We have successfully used a modified method for evaluating the adequacy of laser treatment coverage of choroidal neovascular membranes. Our technique is simpler and less time consuming.

A black and white transparency is obtained immediately after laser treatment by using instant slide film (Polagraph 35 mm, HC-135-12). The treated area appears white. This is overlaid on the fluorescein angiogram frame negative, which demonstrates the extent of the neovascular membrane. All landmarks and blood vessels are aligned and the two film strips are taped together. By using a 60-W incandescent bulb for illumination (traditional light box illumination is inadequate) and a 20-diopter lens for magnification, the laser treatment (white) can be seen outlining the choroidal neovascular membrane (black). Untreated portions of the membrane can be identified easily by using this technique. When adjacent blood or retinal pigment epithelial atrophy is noted, interpretation by using this technique is less accurate, and the method used by the Macular Photocoagulation Study is preferred. We have successfully used our technique in 15 cases.

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Obstructive Sleep Apnea and the Floppy Eyelid Syndrome

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The floppy eyelid syndrome is characterized by the presence of an easily everted upper eyelid associated with keratoconjunctivitis.[1-3] Typically, patients with floppy eyelid syndrome are overweight males who often display the habitus characteristic of a potentially fatal disorder that affects head and neck tissues, obstructive sleep apnea. Although reference to a "pickwickian disorder" has been made in the description of at least one patient with floppy eyelid syndrome,[3] this report focused on the ophthalmic manifestations of floppy eyelid syndrome and not on an associated respiratory disorder. I examined three patients who had both floppy eyelid syndrome and obstructive sleep apnea.

Case 1

A 32-year-old man had a four-year history of conjunctivitis in both eyes and mild right upper eyelid blepharoptosis. Examination disclosed upper eyelid eversion upon application of mild upward traction (Fig. 1) and a fine superior tarsal papillary conjunctivitis. The patient was obese with a short bullneck appearance, and results of polysomnographic studies were consistent with obstructive sleep apnea.

Fig. 1 (Woog). Case 1. Upper eyelids evert easily with gentle upward traction.
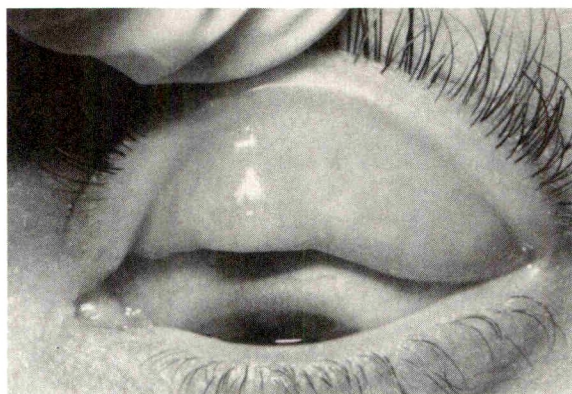
Fig. 2 (Woog). Case 2. Everted left upper eyelid demonstrates velvety tarsal papillary conjunctivitis.

Case 2

A 22-year-old man had a six-year history of recurrent conjunctival injection in the left eye. Examination showed keratoconjunctivitis in the left eye with corneal vascularization and an easily everted left upper eyelid (Fig. 2). The patient's parents noted that he snored loudly, and characteristically slept on his left side with his left upper eyelid everted. Sleep evaluation findings were consistent with obstructive sleep apnea.

Case 3

A 45-year-old obese man had previously undergone uvulopalatopharyngoplasty for obstructive sleep apnea. The patient had a three-year history of irritation and injection in both eyes, particularly prominent upon awakening. Easily everted upper eyelids with a mild superior tarsal conjunctivitis were noted upon examination.

Obstructive sleep apnea is characterized by periods of apnea and hypopnea during sleep, which occur as a result of upper airway obstruction.[4] Patients with obstructive sleep apnea demonstrate partial or complete collapse of the pharynx during inspiration, with symptoms ranging from loud snoring to unrefreshing sleep, daytime somnolence, morning headaches, and personality disturbances. Numerous medical problems have been associated with obstructive sleep apnea, including systemic and pulmonary hypertension, cardiac arrhythmias, and an increased frequency of automobile accidents.[5]

Although the cause of pharyngeal collapse in

obstructive sleep apnea is poorly understood, it has been suggested that redundancy or abnormal laxity of oropharyngeal tissues may be involved in the pathogenesis of this disorder.[4] It is possible that similar defects in the tarsal plate or the canthal tendons may be important in the development of floppy eyelid syndrome. The concurrence of obstructive sleep apnea and floppy eyelid syndrome in my patients might suggest a common underlying abnormality involving the connective tissues of the head and neck. Recognition of a predilection for upper airway obstruction in at least one subset of patients with floppy eyelid syndrome may not only aid in patient treatment during corrective eyelid surgery, but may also ensure appropriate referral of these patients for further medical examination and therapy.

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Magnetic Resonance Imaging of Superior Oblique Muscle Atrophy in Acquired Trochlear Nerve Palsy

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Isolated trochlear nerve palsy is the most common cause of acquired vertical strabismus in adults.[1] The cause often remains unknown despite appropriate investigation.[2,3] Most patients recover spontaneously within four months.[3] Occasionally, patients with idiopathic trochlear nerve palsy do not regain superior oblique muscle function. In these cases, unremitting vertical diplopia without clear cause may prompt neuroimaging studies.

A 62-year-old man reported the onset of vertical diplopia four years before an examination. To achieve fusion he assumed a left head

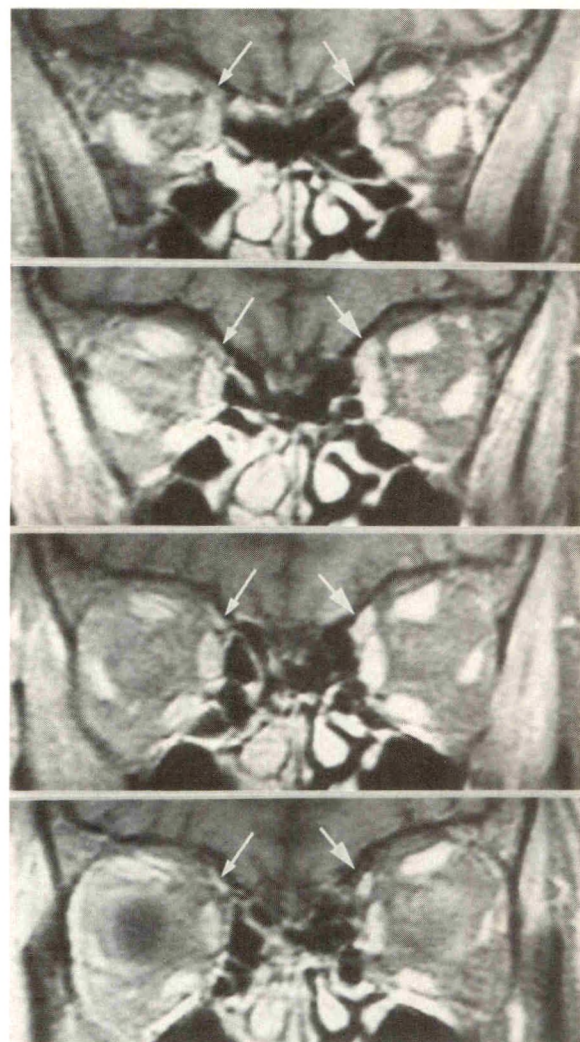**Fig. 1** (Horton and associates). Serial 3-mm, T_1-weighted, fat-saturation, gadolinium-enhanced images show selective atrophy of the right superior oblique muscle (small arrows). The left superior oblique muscle is normal in size (large arrows).

tilt and used spectacles with vertical and base out prisms. For three months the patient noted constant diplopia while reading through his bifocal segment. Without correction the patient had 14 prism diopters of right hypertropia and a small esotropia in primary gaze. The right hypertropia increased to 20 prism diopters on downgaze. The hypertropia also increased on left gaze and right head tilt. Excyclotropia was noted by Maddox rod testing.

We obtained a magnetic resonance scan of the brain and orbits to search for a structural lesion involving the right trochlear nerve. None was found. However, views through the orbits disclosed atrophy of the right superior oblique muscle. In T_1-weighted coronal sections from the orbital apex to the back of the globe the profile of the right superior oblique muscle appeared severely reduced in size when compared with the normal left superior oblique muscle (Fig. 1). Atrophy was also apparent in the axial plane (Fig. 2).

Usually the diagnosis of trochlear nerve palsy can be made securely by clinical examination alone. Ocular myasthenia, however, can occur infrequently as a chronic, isolated extraocular muscle paresis. In myasthenia an affected muscle should appear essentially normal in caliber on neuroimaging. In acquired vertical strabismus from a supranuclear lesion extraocular muscle size will also remain normal.

Injury to the motor nerve innervating a striated muscle can result in loss of up to 80% of muscle bulk because of the wasting of individual muscle fibers.[4] This process is characterized by shrinkage of sarcomeres, loss of myofibrils, and replacement by fatty tissue. The degree of muscle atrophy seen in our patient is compatible with denervation atrophy. Absence of the

Fig. 2 (Horton and associates). In axial section the right superior oblique muscle belly (small arrow) is reduced to one third the size of the left superior oblique muscle (large arrow).

superior oblique muscle has been shown previously by computed tomographic scans in congenital superior oblique muscle palsy.[5] Attention to muscle size within the orbit can be of diagnostic value when performing magnetic resonance scanning on a patient with persistent vertical strabismus. Atrophy of the superior oblique muscle confirms palsy of its nerve. When muscle atrophy is severe, functional recovery is improbable.

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Cavernous Hemangioma of the Lacrimal Sac

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A 59-year-old man was examined for the gradual onset of tearing and an enlarging mass in the right medial canthal area. The mass had assumed a dark blue color. The patient had neither pain nor bloody tears.

The results of a preoperative examination disclosed a blue mass, 1 cm in diameter, extending above the level of the medial canthal tendon. It did not involve the overlying skin. Probing of the proximal lacrimal system demonstrated obstruction of both canaliculi. Irriga-
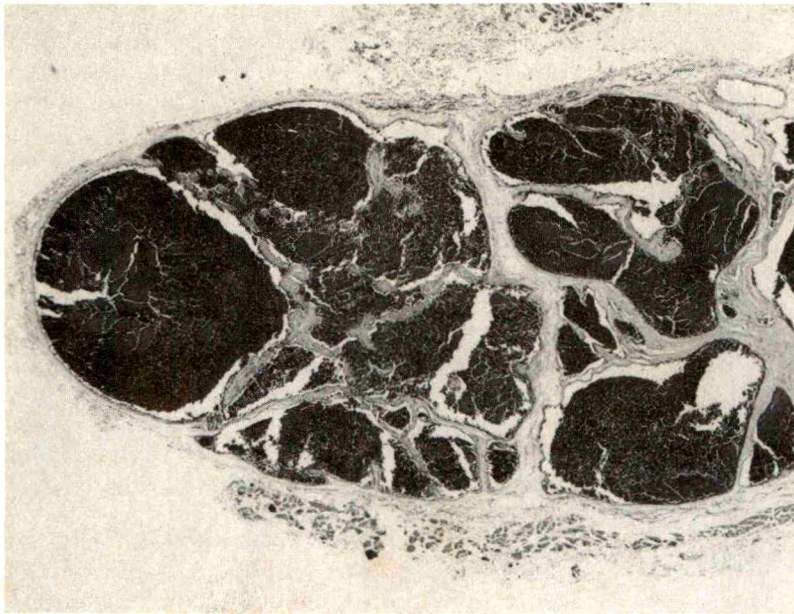
Figure (Ferry and Kaltreider). The tumor consists of large, irregular, blood-filled channels lined by flattened endothelium and separated by fibrous septa (hematoxylin and eosin, × 25).

tion of the inferior canaliculus produced reflux from the inferior punctum around the irrigating cannula, and there was no escape of fluid from the superior punctum. Irrigation of the superior canaliculus produced reflux from the superior punctum around the irrigating cannula, but no fluid emerged from the inferior punctum. This suggested involvement of both canaliculi and of the common canaliculus by lacrimal sac tumor. A computed tomographic scan supported the clinical diagnosis of tumor located in the area of the lacrimal sac. The mass did not erode the adjacent bone.

A dacryocystorhinostomy incision was made, and the medial canthal tendon was reflected laterally to expose the lacrimal sac. A blue, vascular, frambesiform (raspberry-like) tumor involving the sac's fundus was identified. The mass and the upper two thirds of the sac were dissected and removed as a whole. The lower portion of the sac and the proximal nasolacrimal duct appeared free of tumor but were resected in a quest for tumor-free margins at the plane of surgical transection. Conjunctival dacryocystorhinostomy, with placement of a Jones tube, was then performed. On histopathologic examination the lesion was a cavernous hemangioma (Figure).

Tumors of the lacrimal sac are rare. Only some 200 cases have been reported.[1,2] Epithelial tumors of the sac are far more common than are those of mesenchymal origin. Hemangiomas of the lacrimal sac are extremely rare. In the text published in 1974, Duke-Elder and

MacFaul[1] listed the following individual cases: capillary angioma, angiofibroma, hemangioendothelioma, hemangiopericytoma, glomus tumor, and Kaposi's sarcoma. They also included two cases of telangiectatic granuloma from earlier published reports. To the cases listed in Duke-Elder's text, one must add the angiosarcoma reported by Harry and Ashton,[3] the capillary hemangioma described by Jamieson,[4] and the hemangiopericytoma reported by Carnevali and associates.[5]

Ni and associates[2] reported 82 primary tumors of the lacrimal sac that had been accessioned from 1955 through 1980 in the Eye Pathology Laboratory of the Eye, Ear, Nose and Throat Hospital of the Shanghai First Medical College. They regarded all of them as having originated in the lacrimal sac, although it is possible that the sac may have been secondarily invaded by a paranasal sinus tumor in some instances. Of these tumors, 74 were malignant. None of these 74 tumors was of vascular origin, and all but three developed from epithelium. The remaining eight cases were benign, and only one of them (a hemangiopericytoma) was of vascular origin.

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The Use of Eye Pads After Cataract Surgery

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The application of an eye pad and a protective shield after cataract surgery is a generally accepted practice that had been suggested as early as 800 B.C.[1] However, little scientific information exists to support its use. A survey of cataract surgeons in the United Kingdom in 1972 showed that only eight of 150 respondents used a shield alone.[2] A recent report in the same publication compared a patched to an unpatched (shield only) group of patients after cataract surgery.[3] Differences in the infection rate and the presence or absence of discharge were studied. The results showed no difference between the two groups. Aside from these reports, a search of the literature disclosed that this subject has received little attention.

To evaluate the need for eye pads after cataract surgery, I undertook a study comparing a group of cataract surgery patients in whom eye padding was used beneath a shield, to a group in whom a shield alone was used.

Over a six-month period of time, the first two cataract patients on the surgical schedule each week were included in the study. A coin toss was used to determine whether the first patient was to have a pad or not and the second patient had the alternative. Of the 26 patients in each group, one patient in each group had surgery under general anesthesia; otherwise all cases were performed with retrobulbar anesthesia and facial nerve block. In each group all procedures were extracapsular with implanting of a posterior chamber intraocular lens. The numbers of phacoemulsification and standard extracapsular procedures were equal in the two groups. I evaluated postoperative conditions that might have been influenced by the presence or absence of an eye pad: epithelial defects, infection, intraocular pressure less than or equal to 8 mm Hg or greater than or equal to 35 mm Hg, wound leak, and hyphema. Responses were sought to the following questions: excessive tearing, inability to sleep, pain (greater than 60 mg codeine), severe foreign body sensation, and photophobia.

Possible mechanical benefits of patching an eye after cataract surgery include stabilizing the wound, preventing infection, and preventing epithelial defects because of inability to close the eyelid after facial nerve block. Other reasons to consider eye pads after cataract surgery are for comfort and to absorb secretions. Objective data were recorded by me, and subjective responses were obtained by an office assistant unaware of the purpose of the study or which patient had received the eye pad.

In the group with eye pads, one patient had a small epithelial defect, two had applanation intraocular pressure greater than 35 mm Hg, and one had an intraocular pressure less than 8 mm Hg. In the group without eye pads, two patients had intraocular pressures less than 8 mm Hg. There were no infections, hyphemas, or wound leaks. Subjectively, responses to all questions were negative. The results thus showed no apparent difference objectively or subjectively between the two groups.

Laws and associates[3] also found no objective difference in infection rate or wound stability. Extracapsular surgery was performed in that study, but the method of anesthesia was not specified. One might expect that many of the patients had general anesthesia for cataract surgery because this is a more common practice in the United Kingdom. I used a facial nerve and retrobulbar block 96% of the time, which might have led to corneal epithelial desiccation with a shield alone. This was not the case. My data support the concept that there are few, if any, medical reasons to use eye pads after cataract surgery as it is performed today. This is particularly true if general anesthesia or peribulbar anesthesia is used, which may allow the

patient at least some vision in the operated on eye on the day of surgery.

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Penetrating Keratoplasty in Ectodermal Dysplasia

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Ectodermal dysplasia is a rare systemic disturbance in the development of ectoderm. When associated with ectrodactyly and cleft palate syndrome, it displays autosomal dominant inheritance with variable expression[1] and is associated with normal intelligence and longevity. Other systemic abnormalities observed with ectodermal dysplasia may include skin roughening, coarse dry hair, abnormal dental development, decreased tearing, punctal atresia, and sweat gland deficiency.[2,3] Ocular findings may include progressive corneal scarring, thinning, and neovascularization, which may lead to severe visual impairment.[3] We treated a mother and son with ectodermal dysplasia, ectrodactyly, and dense corneal scarring, who underwent successful penetrating keratoplasty after spontaneous corneal perforation.

Case 1

A 45-year-old woman had ectrodactyly of the feet and hands, as well as dry skin, coarse dry hair, and dental anomalies since birth. She had progressive corneal opacification and, by 1987, had extensive corneal scarring in both eyes with central thinning and neovascularization. Visual acuity was counting fingers in both eyes with Schirmer tests of R.E.: 20 mm and L.E.: 35 mm. In March 1989, the patient had a right, spontaneous, corneal perforation with a flat anterior chamber. An emergency penetrating keratoplasty was performed. Two months postoperatively, the patient developed staphylococcal ulcerative keratitis with subsequent corneal perforation in the graft, which necessitated a repeat penetrating keratoplasty. Ten months postoperatively, the patient had a clear cornea and 20/100 visual acuity in the operated on eye.

Case 2

The 23-year-old son of Case 1 had normal eyes at birth but gradually developed extensive corneal scarring, thinning, calcific band keratopathy, and neovascularization (Figure). By 1985, visual acuity was counting fingers in both eyes with Schirmer tests of R.E.: 35 mm and L.E.: 30 mm. The patient had recurrent epithelial defects and corneal melting, which led to a right, spontaneous, corneal perforation. The patient underwent a penetrating keratoplasty with tarsorrhaphy in February 1988. The postoperative course was uneventful, except for a mild recurrent erosion that has necessitated the use of a bandage contact lens. Twenty-two months postoperatively, the graft had peripheral scarring and neovascularization but was clear centrally, with 20/60 visual acuity in the operated on eye.

The ocular manifestations of ectodermal dysplasia include progressive corneal stromal scarring, neovascularization, and thinning,[2,3] which
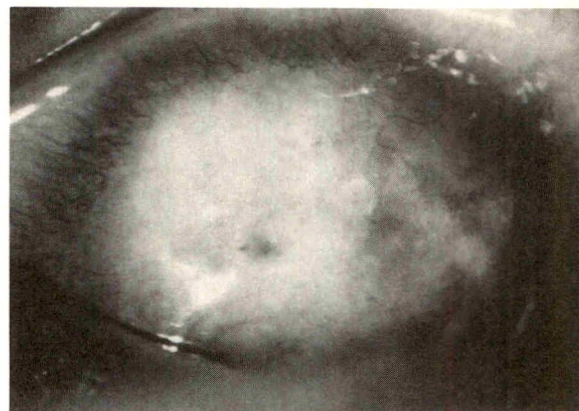

Figure (Mader and Stulting). Case 2. The right cornea before spontaneous perforation showing pronounced scarring.

may lead to corneal perforation.[1] Although neither patient we treated had a cleft palate, both patients probably have variants of the ectrodactyly, ectodermal dysplasia, and cleft palate syndrome. In a previous report of ectodermal dysplasia, a penetrating keratoplasty[3] was unsuccessful in the treatment of this condition. In contrast to our patients, however, this report involved a patient with decreased tear production. Our patients' extensive corneal findings with normal to high Schirmer test results support Baum and Bull's[3] hypothesis that corneal anomalies in ectodermal dysplasia are caused by primary ectodermal defects as opposed to the effects of drying. We believe that patients with advanced corneal changes associated with ectodermal dysplasia and normal tear function may benefit from a penetrating keratoplasty.

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Cryptococcal Keratitis After Keratoplasty

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Cryptococcus is a systemic fungus that usually occurs as an asymptomatic pulmonary infection and less commonly as a meningoencephalitis. *Cryptococcus neoformans* is the causative agent of cryptococcosis. Ocular disease frequently occurs by direct extension from the meninges and manifests as papilledema, optic atrophy, and extraocular muscle paresis.[1] Chorioretinitis and endophthalmitis are usually blood-borne infections in immunocompromised hosts.[2-4] We treated a patient who had cryptococcal keratitis involving the superficial cornea two months after keratoplasty.

A 72-year-old man with a history of aphakic bullous keratopathy underwent a penetrating keratoplasty in the right eye with anterior vitrectomy and synechiolysis. Two months postoperatively the patient developed mild foreign body sensation in the right eye. He was taking dexamethasone solution twice daily and chloramphenicol once daily. Visual acuity, which was counting fingers preoperatively, had improved to 20/400. Intraocular pressure was 23 mm Hg. Limbal injection at the 11 o'clock meridian with an area of central depression in the peripheral host cornea adjacent to the corneal graft showed a gray-white infiltrate with some fine streaks of radiating lines limited to the epithelium, about 3.0 mm in size (Fig. 1). Corneal scrapings were performed, as well as cultures on blood, chocolate, and Sabouraud's agar and thioglycollate broth, which all showed positive results for *C. neoformans*. Papanicolaou smear showed myriads of yeast organisms with budding forms and great variations in size with giant cells (Fig. 2).

The patient responded to therapy with topical miconazole, 10 mg/ml eyedrops hourly for two weeks, which was tapered slowly. Sensitivities obtained from the New York State Laboratory were as follows: amphotericin B, 0.0625 mg/ml; natamycin, 1.9 mg/ml; miconazole, 1.25 mg/ml; and ketoconazole, 1.25 mg/ml.
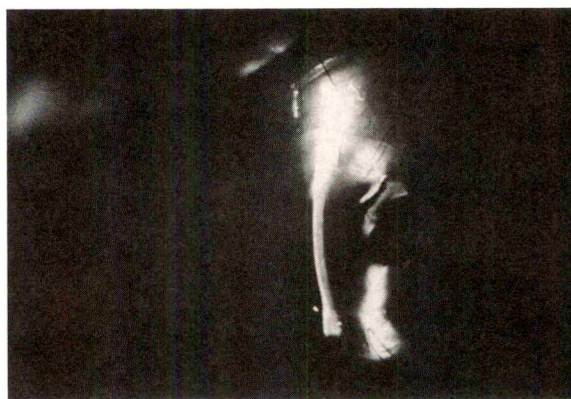

Fig. 1 (Perry and Donnenfeld). Slit-lamp photograph showing superficial white granular lines radiating out from the 11 o'clock meridian peripherally onto the donor cornea.
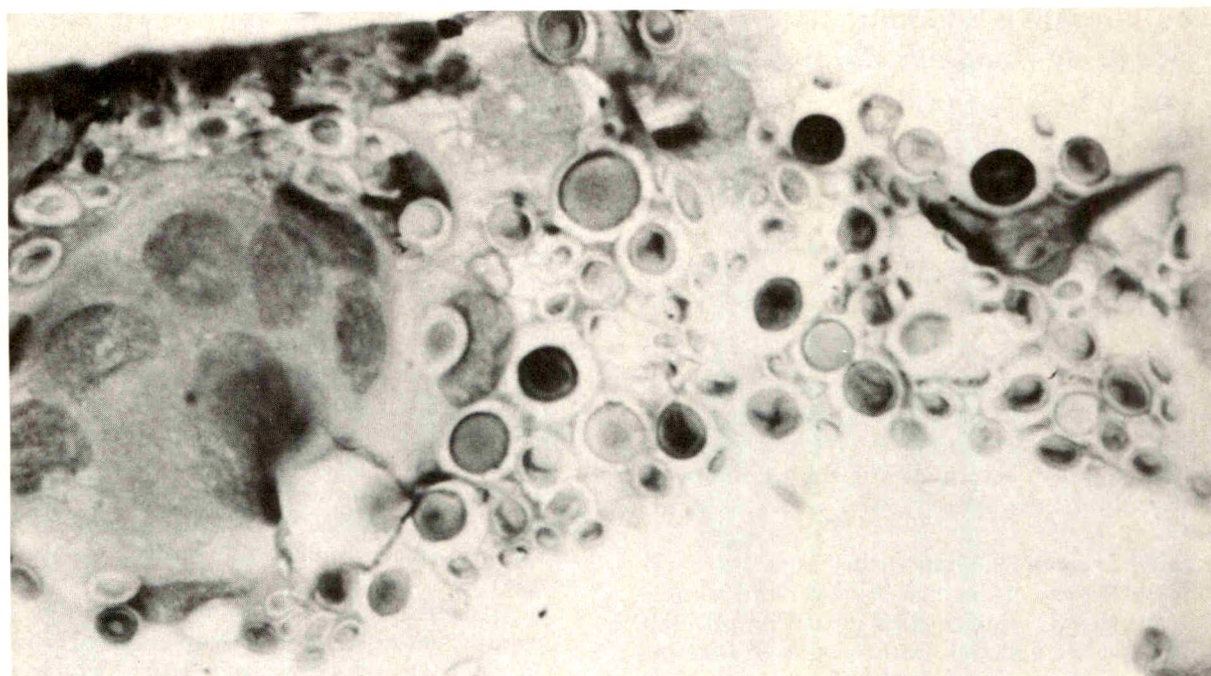
Fig. 2 (Perry and Donnenfeld). Granulomatous reaction characterized by giant cell and intracellular position of *C. neoformans* organisms. Note numerous budding forms along with more mature forms showing thick capsule (Papanicolaou, × 600).

Results of a culture of the donor rim and Dexsol medium (1% dextran and 1.35% chondroitin sulfate) were both negative. The donor died of myocardial infarction and showed no signs of the disease. We were unable to determine a source for the patient's cryptococcal keratitis. The patient with the other donor cornea has done well.

Cryptococcal keratitis is a rare complication in patients who have undergone keratoplasty, although the central corneal graft may be considered a compromised host secondary to denervation and treatment with topical corticosteroids. Beyt and Waltman[5] reported *C. neoformans* endophthalmitis after corneal transplant. They theorized the donor cornea was responsible for transmission of the infection because the donor had died of systemic cryptococcosis, but there was no direct evidence of this in the graft. Their patient also did well for two months. The fellow cornea showed no infection.

Laboratory identification of *C. neoformans* is readily performed by direct examination of a wet mount. In our case, Papanicolaou preparation was dramatically positive, followed rapidly by culture confirmation within 48 hours. We believe the use of laboratory analysis provided us with rapid diagnosis of a clinically unsuspected organism, *C. neoformans*. The performance of smears cannot be overemphasized in the examination of patients with keratitis after keratoplasty.

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Postoperative Endophthalmitis Caused by *Wangiella dermatitidis*

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Wangiella dermatitidis is a saprophytic dematiaceous fungus that can cause chronic dermal and subcutaneous infections in humans. Visceral infections are rare.[1,2] We treated a patient who developed a recalcitrant endophthalmitis caused by *W. dermatitidis* after cataract extraction.

A 75-year-old woman with diabetes was referred because of decreased vision and a painful left eye 17 weeks after an uncomplicated intracapsular cataract extraction with implantation of an anterior chamber intraocular lens. The patient had been taking topical corticosteroids postoperatively for persistent inflammation. Visual acuity decreased from 20/60 to counting fingers over a five-day period. Signs of endophthalmitis prompted an immediate pars plana vitrectomy. A Gram stain of the vitreous demonstrated fungal hyphae; 5.0 µg of intravitreal amphotericin B was given. Two additional vitrectomies with injection of amphotericin B and removal of the intraocular lens were performed over the next two months as the inflammation worsened. Cultures from the eye grew *W. dermatitidis*. The blind eye was enucleated because the patient became intolerant to pain.

Pathologic examination of the globe disclosed a large abscess straddling the pupil (Fig. 1). Degenerating neutrophils were surrounded by epithelioid histiocytes and multinucleated giant cells (Fig. 2). Acute and chronic inflammatory cells and granulation tissue extended into the anterior chamber and vitreous. Branching, septate fungal hyphae (3.0 to 5.0 µm in diameter) were found in the peripheral aspect of the abscess (Fig. 1, inset). No organisms were present in or near the limbal incision from cataract surgery.

Ocular infection caused by *W. dermatitidis* is unusual. The organism has been cultured from an infected corneal graft in one patient who was successfully treated with topical natamycin 5%, amphotericin B 0.5%, and a second penetrating keratoplasty.[3]

The source of an infection caused by an organism that is not part of the human flora can be difficult to determine. The absence of limbal wound involvement and the location of the abscess centrally in the pupil of this patient suggest that the organism was probably intro-

Fig. 1 (Margo and Fitzgerald). A large intraocular abscess straddles the pupil, which bulges into the anterior chamber and vitreous (hematoxylin and eosin, ×4.3). Inset, 3.0- to 5.0-µm branching fungal hyphae are present in the peripheral part of the abscess (Gomori methenamine-silver, ×440).
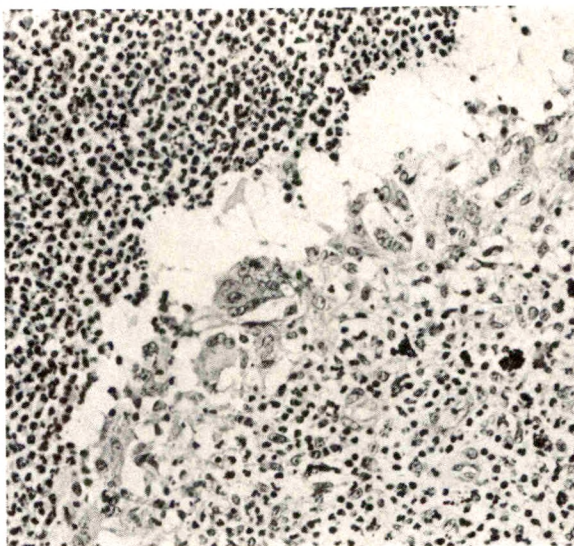

Fig. 2 (Margo and Fitzgerald). Neutrophils (to the right) within the abscess are surrounded by a palisade of epithelioid histiocytes and multinucleated giant cells (hematoxylin and eosin, ×220).

duced into the eye at the time of cataract surgery. Fungal contamination of either the irrigating solution or the implanted lens are possible but difficult to verify retrospectively in an isolated case.[4] Dematiaceous fungi have been recovered from unopened bottles of balanced salt solution.[5] To date, this patient's infection appears to be an isolated case, the source of which has not been determined.

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Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Safety of Fluorescein Angiography During Pregnancy

EDITOR:
    In the article "Safety of fluorescein angiography during pregnancy" by L. S. Halperin,

R. J. Olk, G. Soubrane, and G. Coscas (Am. J. Ophthalmol. 109:563, May 1990), although the authors' conclusion, that it may be reasonable to perform fluorescein angiography on a pregnant patient who has a sight-threatening vasculopathy, may be valid, we are concerned that their article does not establish the safety of the use of fluorescein angiography during pregnancy. We cannot agree with the conclusion that "fluorescein angiography does not result in a high rate of birth anomalies or complications when performed on a pregnant patient," since this conclusion is not supported by the data submitted by the authors. When evaluating the potential teratogenicity of agents in pregnancy, there are two primary concerns: the effect on organogenesis and the effect on the pregnancy itself. To evaluate the possible teratogenicity during organogenesis, one should evaluate exposures during the first trimester. In their review of either 399 or 403 respondents (the article is internally inconsistent), 90 specialists acknowledged performance of at least one fluorescein angiogram on at least one pregnant woman during the preceding ten years. Forty-five specialists could not provide any information on those subjects, and nine additional specialists could not be reached for further information. Fifty-four (60%) of these 90 specialists who stated that they had performed fluorescein angiography were unable to provide adequate information. Thus, apparently, more than half of the potential study sample was lost or unavailable.

The article does not state whether any attempt was made to assess the medical status of outcomes of possible pregnancies among those women of reproductive age who were not knowingly pregnant and yet had fluorescein angiography performed (patients of the remaining 309 or 313 specialists, depending on one's reading of the article). Thus, a control population for this study might well have been the outcomes of pregnancies among women who inadvertently received fluorescein because they did not know that they were pregnant or they were not specifically asked whether they might be pregnant at the time of the procedure.

The authors ascertained only 19 pregnancies with first trimester exposures, as well as 22 pregnancies that may have had multiple exposures, including a period during the first trimester. Thus, somewhere between 19 and 41 pregnancies were exposed to intravenous fluorescein during the first trimester. Because of

this relatively small number of exposures in the first trimester, it is difficult, if not impossible, to detect an increase in the rate of malformations compared to an unspecified control population.

Since the outcome of pregnancy after fluorescein exposure was solicited retrospectively and by questionnaire, it is difficult to determine the extent of the ascertainment and the diligence of the catamnesis. How often, for example, did the ophthalmologists update information on the outcome of pregnancy and on neonatal and postnatal development from their obstetric or pediatric colleagues to determine whether these infants were normal? Did that purported normality extend through the period of primary education, where subtle defects in learning abilities might become first apparent? Without this information, there could be either positive or negative bias of ascertainment. This interpretation is complicated further by this retrospective survey.

Since 40 pregnant women were examined for diabetic retinopathy, and since women with insulin-dependent diabetes mellitus are at well-defined and significantly increased risk for various adverse outcomes of pregnancy, such as stillbirths, obstetric complications, and congenital malformations, these data should be analyzed separately.

It is unclear why the authors decided to exclude the four neonatal or fetal deaths from their study. Although these may not be related to the exposure to fluorescein, it is unclear whether one fetal death and one spontaneous abortion may have occurred from the effect of fluorescein exposure or from the underlying primary medical condition.

Only two offspring were reported to have birth defects. One child was reported to have an undescended testicle, for no apparent reason and without other stated association. The significance of this observation must be considered in the context of the infant's gestational age at the time of exposure, which is not stated. Another infant was described to have syndactyly. However, the authors do not state the type of syndactyly nor whether there was a family history of syndactyly. Since various syndromic associations of syndactyly have been documented, the diligence of ascertainment of other subtle malformations is critical to an understanding of this report; yet these data are missing.

Lastly, without a suitable control group with which to compare their data, so that an adequate population-based or case-control study

can be done, the authors do not provide sufficient information to document incontrovertibly the safety of fluorescein angiography in pregnancy. Until these or other investigators are able to provide complete and prospective information, perhaps comparing the outcome of pregnancies in which fluorescein angiography was done and pregnancies in which it was indicated but not performed, the benefits and the risks of this procedure must be discussed individually with pregnant women and should not be performed arbitrarily. If the expected risk caused by fluorescein directly is low, then the sample sizes will need to be large to detect a statistically significant difference in the two populations. We hope that these better data will be forthcoming in the future. We look forward to a major national or international effort to design such a prospective protocol for this agent, which so long has been considered generally regarded as safe.

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—————————— **Reply** ——————————

EDITOR:
Drs. Greenberg and Lewis are correct in pointing out a transcription error in our abstract, which should have indicated that "403 specialists responded . . . " and "313 had never performed fluorescein angiography . . . ."

The text was clear in pointing out that a total of 41 pregnancies were exposed to intravenous fluorescein during the first trimester (19 only in the first trimester and 22 with exposure in all three trimesters). It is clearly stated why we excluded the four neonatal or fetal deaths: two were because of complications related to eclampsia; one occurred months after injection of fluorescein; and "one spontaneous abortion occurred three days after fluorescein angiography in a four-week pregnancy of an otherwise healthy woman."

We agree completely with Drs. Greenberg and Lewis that "the benefits and risks of this procedure must be discussed individually with pregnant women and should not be performed arbitrarily." Our concluding paragraph clearly states: "The decision to perform fluorescein angiography on a pregnant patient is left to the physician and patient, who should carefully weigh the risks and benefits of the procedure." We would further emphasize that one of the main purposes of this article was to

provide data that we believe "can be valuable to ophthalmologists who must advise patients who underwent fluorescein angiography before they knew they were pregnant."

We acknowledge that the data collected from this retrospective study have all the known inherent problems of data collected from any retrospective study. Nowhere in our article, however, do we "document incontrovertibly the safety of fluorescein angiography in pregnancy," as Drs. Greenberg and Lewis suggest. We simply restate our conclusions that based on our data and existing animal data, fluorescein angiography does not result in a high rate of birth anomalies when performed on a pregnant patient, and to reiterate: "We believe it is reasonable to perform fluorescein angiography on a pregnant patient when vision is threatened by a choroidal neovascular membrane; fluorescein angiography could affect the patient's treatment or eventual outcome."

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Tight Scleral Flap Trabeculectomy With Postoperative Laser Suture Lysis

EDITOR:

In the article "Tight scleral flap trabeculectomy with postoperative laser suture lysis," by S. Melamed, I. Ashkenazi, J. Glovinsky, and M. Blumenthal (Am. J. Ophthalmol. 109:303, March 1990), the authors pointed out the advantage of tight closure of the scleral flap in trabeculectomy to minimize such common complications as hypotony, flat anterior chamber, and choroidal detachment. A substantial portion of the patients who underwent purposely tight closure of the scleral flap were found to have adequate filtration without the need of laser suture lysis. When the need develops for an increase in aqueous filtration postoperatively, the lamellar scleral flap closure is relaxed by releasing the scleral flap closure suture, which achieves the best of both partial-thickness and full-thickness filtering procedures. The authors are fortunate, however, in being able to achieve lysis of the scleral flap closure suture with either argon or

Nd:YAG laser in all cases. We have encountered at least two cases in which suture lysis could not be achieved with either argon or Nd:YAG laser because of substantial subconjunctival hematoma or unusually thick Tenon's tissue over the scleral flap. Furthermore, premature release of the scleral flap closure suture before satisfactory healing of the conjunctival wound and resumption of normal aqueous humor formation, usually during the first two postoperative days, can result in wound leak and resultant hypotony, flat anterior chamber, and choroidal detachment, which negate the benefits of this technique. This is of particular importance in cases in which wound healing is delayed, as occurs with the adjunctive use of subconjunctival 5-fluorouracil.

Relaxation of the scleral flap closure can be achieved with the use of the releasable suture closure technique.[1-3] This technique has the advantage of being effective even when a laser or a Hoskins contact lens is not readily available, or when the scleral flap suture is obscured by subconjunctival hemorrhage, thick Tenon's tissue, or fibrous proliferation.

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——————— Reply ———————

EDITOR:

We were glad to learn that the concept of tight trabeculectomy with late release of the scleral flap sutures is considered by Drs. Shin, Parrow, and Presberg-Greene to be the preferred method of guarded filtration surgery. It is true that in some cases it is more difficult to visualize the sutures because of thick Tenon's capsule. However, we were able to successfully

lyse all sutures after application of more pressure against the tissue with resultant flattening and clearance of the obstructing layers. Additionally, we found out in later cases that black sutures are lysed easily by the blue-green argon laser, whereas the blue sutures require krypton red laser energy for adequate absorption and cutting effect.

We agree that premature lysis of the sutures may be associated with bleb leak, hypotony, and flattening of the anterior chamber. Based on our experience, however, we have rarely found these complications when laser treatment was performed at least 48 hours after surgery. We believe that this is the minimum time required for the formation of water-tight adhesion of conjunctiva to the corneoscleral limbus.

We agree that the use of subconjunctival 5-fluorouracil should change our approach as the healing process is delayed. We have had some experience with the combination of both treatment modalities, and we usually postpone the laser suture lysis up to seven to ten days postoperatively or at least two days after the final dose of 5-fluorouracil.[1]

The technique reported by us and Savage and associates[2] describes the basic concept of forming a hybrid operation of trabeculectomy that is later turned into a full-thickness filtration. We believe this is a simple method combining the advantages of both procedures with a high success rate. Other similar methods achieving the same results are adequate; however, the most successful method should be adopted.

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Posterior Vitreous Cyst

EDITOR:

In the article "Posterior vitreous cyst," by R. L. Steinmetz, B. R. Straatsma, and M. L. Rubin (Am. J. Ophthalmol. 109:295, March 1990), the authors postulate that the vitreous cysts as remnants of the hyaloid system are only located on the disk. Rochels and I[1] treated a 15-year-old girl with unilateral potato-shaped vitreous cyst, which was attached to the posterior lens surface by a short, threadlike strand and was therefore only slightly mobile. Partially vascularized prepapillary strands were observed in the patient's fellow eye, which led to the impression of impaired retrogression of the primary vitreous.

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Reference

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——————— Reply ———————

EDITOR:

In the article we described clinical features of two patients with unilateral cyst in the posterior vitreous, one of whom was observed for 17 years. One of these two patients had a prominent Mittendorf dot on the posterior surface of the crystalline lens. In the discussion, we noted that some vitreous cysts probably develop from remnants of the hyaloid system and may even be attached to the optic disk by a stalk. Dr. Lisch describes a vitreous cyst attached to the posterior lens surface by a strand and adds support to the concept that vitreous cysts may be derived from remnants of the hyaloid system.

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BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Binocular Vision and Ocular Motility. Theory and Management of Strabismus, ed. 4. By Gunter K. von Noorden. St. Louis, C. V. Mosby, 1990. 557 pages, index, illustrated. $92

Reviewed by ROBERT J. MORRIS
London, England

This is the fourth edition of a text originally co-authored with Dr. Burian in 1974, but revised by Dr. von Noorden ever since. It remains the most comprehensive text in the field of ocular motility and strabismus. Written in a clear, readable style, it offers an unusually rich historical perspective on the subject. The literature is well referenced at the end of each chapter.

As with previous editions, Sections 1 and 2 cover sensorimotor physiology and neuromuscular anomalies of the eye. The sections provide a thorough account of the theoretic aspects of strabismus. The expanded section, "Sensory Signs and Symptoms of Strabismus," covers an area of particular interest to Dr. von Noorden, and it includes an outstanding account of amblyopia. Sections 3 and 4 cover the clinical aspects and principles of treatment of strabismus. In Section 4 the chapter on nonsurgical treatment of strabismus describes optical, pharmacologic, and orthoptic treatment of strabismus, important but often neglected areas of the subject. There is an expanded section on surgical techniques, which is beautifully illustrated, and reflects the author's surgical preferences. One small quibble I have with this section is the omission of Fells modification of the Harada-Ito procedure, which has now become more widely used than the original technique.

There is little to criticize in this book. I feel, however, the section on botulinum toxin therapy should have discussed the physiologic action of the drug and its clinical indications in more detail. Similarly I think the discussion on fourth nerve palsies is brief and should have included more emphasis on the concept of masked bilateral superior oblique palsies. Sadly the book no longer attempts to discuss supranuclear control of eye movements as Dr. von Noorden feels that this is beyond the scope of the book and refers the reader to other sources.

However, these points are minor and this book remains a classic text on strabismus. It should appeal to residents in training as well as to any ophthalmologist with an interest in ocular motility.

Stedman's Medical Dictionary, ed. 25. Baltimore, Williams & Wilkins. 1,784 pages, illustrated. $38.95

Reviewed by MARK J. MANNIS
Sacramento, California

For most physicians, the medical dictionary remains in place on the bookshelf, to be taken down only when a paper is to be written or when the leg of a table needs to be propped up. It is a book that not-so-favorite relatives buy for you when you are accepted to medical school or that you magnanimously purchase for your secretary when you open your practice. It is not, alas, a book that gets worn with use before it gets worn with age. Nonetheless, like just the right Phillips screwdriver, it is absolutely indispensable when you need it.

The 25th edition of Stedman's Medical Dictionary is billed in the preface as "user friendly." Although dictionary use does not generally require any tutoring, this volume begins with a section on how to use the dictionary that includes an explanation of the anatomy of the entries and cross-references, a pronunciation guide, and a key to abbreviations. This is followed by an interesting section on medical etymology. The vocabulary entries are preceded by Stedman's Subentry Locator, an extensive and useful list of subentry terms, mostly adjectives, followed by the primary entries with which they are most commonly used; this section is a handy cross-referencing system.

The vocabulary entries include over 1,700 pages of definitions in clear, readable print. The pages are conveniently tabbed, making the location of words easy and rapid. The vocabulary entries are complemented by numerous illustrations, 24 anatomic color plates, and a large

number of tables. The final section of this reference consists of appendices including comparative temperature scales and equivalents, weights and measures, laboratory reference range values, and a section on blood groups.

Comparison with another popular medical dictionary I received as a student 20 years ago revealed that not much has changed in the format of the modern medical dictionary. Virtually all the components of the new edition were contained in the old. The chief value of this new volume is its updated vocabulary. (One can find "epikeratophakia" but not "capsulorrhexis.") Then again, the basic screwdriver has not changed much, and for this reason, it continues to be supremely useful. Stedman's is a well-executed volume that will be of value to its owner for years to come.

Management of Orbital and Ocular Adnexal Tumors and Inflammations. Edited by Joseph A. Mauriello, Jr., and Joseph C. Flanagan. New York, Field & Wood Medical Publishers, Inc., 1990. 285 pages, index, illustrated. $145

Reviewed by THOMAS C. SPOOR
Detroit, Michigan

Considering the experience and expertise of the editors, this text is well written and profusely illustrated, utilizing the clinical and computed tomographic histopathologic format often popular on board examinations, and it is invaluable for understanding orbital disease processes.

The book is divided into eight sections. Chapter 1 describes patients with orbital disorders and reviews the various disease processes affecting the orbit. Orbital and adnexal problems are divided into six categories, which are the subjects of subsequent chapters: orbital inflammatory disease, adult orbital tumors, pediatric orbital tumors, lacrimal gland inflammation and tumors, lacrimal sac inflammations and tumors, and eyelid tumors and inflammation. An additional chapter reviews orbital surgical techniques for both tumor removal and dysthyroid orbitopathy (orbital decompression and eyelid reconstruction). Basic and advanced eyelid reconstruction is well reviewed in the final chapter, "Tumors and Inflammations of the Lids."

This book provides an excellent review of the plethora of orbital and adnexal disease processes, as well as the surgical techniques used to treat them. Additionally, each chapter is well referenced. It is a welcome addition to my library of oculoplastic, orbital, and neuro-ophthalmic references and should be added to yours.

Fitting Guide for Rigid and Soft Contact Lenses. A Practical Approach, ed. 3. Edited by Harold A. Stein, Bernhard J. Slatt, and Raymond M. Stein. St. Louis, C. V. Mosby, 1990. 613 pages, index, illustrated. $55.95

Reviewed by R. LINSY FARRIS
New York, New York

Harold Stein and Bernhard Slatt have been joined by Raymond Stein and several new authors to produce an enlarged and up-to-date edition of Fitting Guide for Rigid and Soft Contact Lenses. The new chapters include examination of the tear film, contact lens materials and manufacturing, contact lens and ocular allergy, current care systems, and verification of contact lens orders. The new chapters by authors such as Allansmith, Morgan, Josephson, and Halberg are good additions to this practical guide of contact lens fitting.

Basic information necessary for fitting contact lenses in a safe and effective manner is the real value of this book. The safety of contact lenses is considered a major issue in patient selection, and an examination of the patient discloses factors against or in favor of successful wear. Not only patient selection but the choice of contact lens is the responsibility of the fitter. The text contains fitting methods for soft and rigid lenses and considers various methods as well as the advantages and disadvantages of different lens types. Difficult fittings, such as for patients with keratoconus and presbyopia, complications, and treatment of ocular allergy associated with extended-wear contact lenses are given special treatment in separate chapters. Many ideas and answers are provided in these pages. I particularly like the practical information provided in the chapter on managing and starting a contact lens practice in the chapter on cosmetics and contact lens wear.

This improved text of directions and explanations from experienced clinicians has abundant

useful information; however, I would like to see references provided at the end of each chapter. The supplementary reading list at the end of the book does not include key references mentioned in the text. Many will be interested in this concise presentation of contact lens fitting, which introduces the subject primarily from the experience of one group but is nevertheless representative of most fitters.

Books Received

Complications de la Chirurgie du Segment Anterieur. By Luc Durand and Carole Burillon. Mexico, Masson, 1989. 521 pages, index, illustrated. (No price given)

This is a major summary of the things that can go wrong when surgery is done on the anterior segment of the eye. The first 12 chapters deal with the way the eye responds: bleeding, scarring, increased intraocular pressure, inflammation, endothelial ingrowth, infection, and so on. The remaining chapters cover the specific complications of surgery for cataract, glaucoma, corneal grafts, and keratorefractive surgery. Chapters on posterior segment complications of anterior segment surgery and the complications of anesthesia are included.

Conjunctival Melanoma in The Netherlands. A Clinico-pathological and Follow-up Study. By D. de Wolff-Rouendaal. Den Haag, The Netherlands, CIP-Gegevens Koninklijke Bibliotheek, 1990. 175 pages, illustrated. (No price given)

A thoughtful monograph on flat pigmented lesions of the conjunctiva based on material collected in The Netherlands over a period of 30 years offers treatment guidelines.

The Book List

Atlas of Vitreoretinal Surgery. By H. MacKenzie and Felipe I. Tolentino. New York, Thieme Medical Publishers, 1990. 274 pages, index, illustrated. (No price given)

Current Opinion in Ophthalmology, vol. 1, No. 1. By George W. Weinstein. Philadelphia, Current Science, 1990. 102 pages, index, illustrated. $45

Current Opinion in Ophthalmology, vol. 1, No. 2. By George W. Weinstein. Philadelphia, Current Science, 1990. 208 pages, index, illustrated. $45.

Electrodiagnostic Testing of the Visual System. A Clinical Guide. By Ronald E. Carr and Irwin M. Siegel. Philadelphia, F. A. Davis Company, 1990. 188 pages, index, illustrated. $55.

For My Patient. Cataract. San Francisco, Pacific Medical Press, 1990. Softcover, 29 pages, illustrated. $2.75

For My Patient. Glaucoma. San Francisco, Pacific Medical Press, 1990. Softcover, 45 pages, illustrated. $2.75

Laser. Its Clinical Uses In eye Diseases. By Ian J. Constable and Arthur S. M. Lim. Singapore, P.-G. Publishing, 1990. 207 pages, index, illustrated. $90

Thyroid Eye Disease, ed. 2. By Devron H. Char. New York, Churchill Livingstone, 1990. 229 pages, index, illustrated. $59.95

ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

Krypton laser photocoagulation for neovascular lesions of age-related macular degeneration. Results of a randomized clinical trial. Macular Photocoagulation Study Group* Arch. Ophthalmol. 108:816, 1990.

MACULAR DEGENERATION, KRYPTON LASER

The Age-Related Macular Degeneration Study—Krypton Laser (AMDS-K) is a multicenter controlled clinical trial designed to determine whether krypton red laser photocoagulation is of value in preventing visual acuity loss in eyes with macular degeneration that have either choroidal neovascularization 1 to 199 μm from the center of the foveal avascular zone or choroidal neovascularization 200 μm or farther from the foveal avascular zone center with blood and/or blocked fluorescence extending within 200 μm of the foveal avascular zone center. Recruitment ended in December 1987 after 247 patients had been assigned to photocoagulation and 249 patients had been assigned to no treatment. At 3 years after randomization, 49% (86/174) of treated eyes, in contrast to 58% (98/169) of untreated eyes, had lost six or more lines of visual acuity. The average visual acuity of treated and untreated eyes at that time was 20/200 and 20/250, respectively. The benefit of laser treatment was largest among patients without evidence of hypertension and diminished to no apparent benefit among patients who had highly elevated blood pressure and/or used antihypertensive medication. Treatment of lesions meeting the AMDS-K eligibility criteria in eyes of patients with no hypertension is recommended. However, treatment cannot be recommended uniformly for patients with definite hypertension having lesions similar to those of patients enrolled in the AMDS-K.—Authors' abstract

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A structural basis for Hering's law. Projections to extraocular motoneurons. Moschovakis, A. K., Scudder, C. A.,* and Highstein, S. M. Science 248:1118, 1990.

HERING'S LAW, EXTRAOCULAR MOVEMENTS

Conjugate eye movements are produced by the coactivation of extraocular muscles in both eyes. According to Hering's law, the two eyes move in a conjugate manner because they receive identical signals from the brain. Until now, however, there has been little information about the anatomic pathways underlying this process.

The premotoneurons responsible for vertical rapid eye movements in alert squirrel monkeys were detected by intracellular recording of electrical activity. After functional characterization of the cells, they were injected with horseradish peroxidase. After 36 to 50 hours of labeling, the brain tissues were studied histologically.

The premotoneurons responsible for rapid upward eye movements innervate regions that contain motoneurons controlling the superior rectus and inferior oblique muscles of both eyes. Conversely, the premotoneurons responsible for rapid downward eye movements innervate regions that contain motoneurons controlling the ipsilateral inferior rectus and the contralateral superior oblique muscles. Thus, premotoneurons project to motoneuron pools that innervate yoked muscles of both eyes. This is qualitative proof for an anatomic system underlying Hering's law in the vertical saccadic system.—Michael A. Kass

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Identification of an inhibitor of neovascularization from cartilage. Moses, M. A., Sudhalter, J., and Langer, R.* Science 248:1408, 1990.

NEOVASCULARIZATION, ENDOGENOUS INHIBITOR, CARTILAGE

Angiogenesis, the process of new capillary formation, is a factor in numerous normal body processes in a variety of diseases including diabetic retinopathy and neovascular glaucoma. Certain tissues, such as cartilage, are resis-

tant to vascular invasion. No single tissue-derived molecule has been described that is capable of inhibiting angiogenesis.

In this study, a protein was extracted from bovine scapular cartilage and purified by precipitation and column chromatography. This protein inhibited angiogenesis in three different experimental models in doses as low as 4 μg. This substance appeared to inhibit proliferation and migration of capillary endothelial cells.

The derived protein appears to be more potent in the chick chorioallantoic membrane assay than any previously described substance or group of substances. The cartilage-derived protein is also an inhibitor of collagenase. Collagenase may play a role in the invasion of capillary endothelial cells during angiogenesis.—Michael A. Kass

*Department of Surgery, Children's Hospital Medical Center, Boston, MA 02139.

The characteristics and mechanisms of visual disturbance associated with anticonvulsant therapy. Remler, B. F., Leigh, R. J.,* Osorio, I., and Tomsak, R. L. Neurology 40:791, 1990.

DIPLOPIA, OSCILLOPSIA, ANTICONVULSANT THERAPY

Visual symptoms, such as diplopia or oscillopsia, are common side effects of treatment with phenytoin and carbamazepine. While antiepileptic medications are known to disturb all functional classes of eye movements, little information exists concerning the correlation of specific visual complaints in individual patients with specific disturbances of ocular motility.

Eight epileptic patients receiving anticonvulsant therapy had recurrent visual disturbances in the form of diplopia and oscillopsia in the horizontal or vertical planes. The symptoms could be ascribed to impaired vergence mechanisms, vertical nystagmus, or abnormalities of the vestibulo-ocular reflex. Other eye movements, such as pursuit and gaze-holding, were also affected, but did not lead to specific complaints. Episodes of visual disturbance were often preceded by ocular or systemic discomfort, after which oscillopsia or diplopia evolved rapidly. The symptoms were stereotyped and unique for each patient, probably reflecting

idiosyncratic susceptibility to the ocular motor side effects of anticonvulsants. Six of the eight patients were taking carbamazepine and phenytoin in combination. The total serum concentrations of the drugs during symptomatic phases were within the therapeutic range. Some patients' symptoms were reduced by titrating or dividing the doses of the drugs.—Michael A. Kass

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The relationship of retrobulbar hematomas to vision in cynomolgus monkeys. Young, V. L.,* Talley, A. R., Pin, P., Trick, G. L., Becker, W., Logan, S. E., and Kraemer, B. A. Plast. Reconstr. Surg. 85:698, 1990.

RETROBULBAR HEMATOMA, ISCHEMIA

An experimental model has been developed to measure the effect of retrobulbar hematomas on functional vision in cynomolgus monkeys. In this model, functional vision was quantitated using flashed evoked visual potentials in five monkeys following creation of retrobulbar hematomas. In one monkey used as a control, functional vision remained impaired for 180 minutes following induction of retinal ischemia by increased intraorbital pressure. In two monkeys in which increased intraorbital pressure was relieved by anterior chamber paracentesis following 15 minutes of retinal ischemia, flashed evoked visual potential promptly returned to baseline level. In two additional monkeys in which increased intraorbital pressure was relieved following 30 minutes of retinal ischemia, flashed evoked visual potentials improved but never returned to baseline levels.

This study demonstrates the usefulness of flashed evoked visual potentials in measuring functional vision in cynomolgus monkeys. This experimental model should prove useful in evaluating the effects of increased intraorbital pressure on functional vision and the effect of intervention on impaired vision due to retrobulbar hematomas. Further studies with larger numbers of animals are needed to clarify these preliminary studies and document longer-term effects of retinal ischemia secondary to retrobulbar hematomas.—Authors' abstract

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Pattern ERG in rats following section of the optic nerve. Berardi, N., Domenici, L.,* Gravina, A., and Maffei, L. Exp. Brain Res. 79:539, 1990.

PATTERN ELECTRORETINOGRAM, OPTIC NERVE

Recent experiments performed in cats and monkeys have shown that the pattern electroretinogram disappears after sectioning the optic nerve. However, most investigations of central nervous system degeneration or regrowth in mammals have utilized the rat as an experimental animal, and there is little information about electrophysiologic tests in the rat.

Flash and pattern electroretinograms were recorded in hooded rats anesthetized with urethane. The pattern electroretinogram was evoked by phase alternating gratings of various spatial frequencies and contrasts. The pattern electroretinogram in response to alternating gratings had a temporal periodicity twice the stimulus temporal frequency and its waveform was approximately sinusoidal for frequencies beyond 2 Hz. In eight rats, the intraorbital portion of the optic nerve was severed and the animals were observed with electrophysiologic tests over time. Sectioning of the optic nerve led to the progressive disappearance of the pattern electroretinogram. By four months after surgery, the pattern electroretinogram was almost unrecordable while the flash electroretinogram was unaffected.

Thus, the pattern electroretinogram appears to be a useful tool to investigate the functional integrity of retinal ganglion cells in rats.—Michael A. Kass

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Developing eyes that lack accommodation grow to compensate for imposed defocus. Schaeffel, F., Troilo, D., Wallman, J.,* and Howland, H. C. Vis. Neurosci. 4:177, 1990.

EMMETROPIA, DEVELOPMENT, ACCOMMODATION

The vertebrate eye normally grows so that its length is proportionate to the focal length of its optical system. Since neonates in many species are not emmetropic, some process must direct postnatal growth of the eye in the direction of emmetropia. A number of investigators have postulated that the act of accommodation may provide the mechanical change necessary for adjusting the growth of the eye. To test this hypothesis, 3- to 5-day-old chicks had bilateral electrolytic lesions of the Edinger-Westphal nuclei. Animals without accommodation and normal control chicks were then fitted with convex spectacle lenses (+2 or +4 diopters) or concave lenses (−4 or −8 diopters). The refractive state of the chicks was monitored by infrared photoretinoscopy. At 30 days of age the chicks had photokeratometry and A-scan ultrasonography. The eyes were then excised and the axial lengths measured directly.

Normal control chick eyes and eyes from chicks with bilateral lesions of the Edinger-Westphal nuclei were able to grow to compensate for spectacle lens-induced myopia or hyperopia. These data indicate that even without accommodation, eyes that are made functionally hyperopic or myopic by spectacle lenses are able to grow at different rates, to compensate partially for the imposed ametropia.—Michael A. Kass

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Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? Haffner, S. M.,* Stern, M. P., Hazuda, H. P., Mitchell, B. D., and Patterson, J. K. JAMA 263:2893, 1990.

DIABETES, CARDIOVASCULAR DISEASE

Although type II diabetes is associated with both microvascular and macrovascular complications, duration of diabetes and severity of glycemia are strongly associated only with the former. Since prediabetic individuals are hyperinsulinemic, and since hyperinsulinemia may be a cardiovascular risk factor, we hypothesized that prediabetic individuals might have an atherogenic pattern of risk factors even before the onset of clinical diabetes, thereby explaining the relative lack of an association of macrovascular complications with either glycemic severity or disease duration. We documented the cardiovascular risk factor status of 614

initially nondiabetic Mexican Americans who later participated in an 8-year follow-up of the San Antonio Heart Study, a population-based study of diabetes and cardiovascular disease. Individuals who were nondiabetic at the time of baseline examination, but who subsequently developed type II diabetes (ie, confirmed prediabetic subjects, n=43), had higher levels of total and low-density lipoprotein cholesterol, triglyceride, fasting glucose and insulin, 2-hour glucose, body mass index, and blood pressure, and lower levels of high-density lipoprotein cholesterol than subjects who remained nondiabetic (n=571). Most of these differences persisted after adjustment for obesity and/or level of glycemia, but were abolished after adjustment for fasting insulin concentration. When subjects with impaired glucose tolerance at baseline (n=106) were eliminated, the more atherogenic pattern of cardiovascular risk factors was still evident (and statistically significant) among initially normoglycemic prediabetic subjects. These results indicate that prediabetic subjects have an atherogenic pattern of risk factors (possibly caused by obesity, hyperglycemia, and especially hyperinsulinemia), which may be present for many years and may contribute to the risk of macrovascular disease as much as the duration of clinical diabetes itself.—Authors' abstract

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Prevalence of undiagnosed eye disease in high-risk diabetic individuals. Sprafka, J. M.,* Fritsche, T. L., Baker, R., Kurth, D., and Whipple, D. Arch. Intern. Med. 150:857, 1990.

DIABETES, DIABETIC RETINOPATHY, CATARACT, GLAUCOMA

This study was designed to measure the prevalence of common ocular disorders in a group of diabetic patients. Five hundred thirty-three diabetic individuals followed up in one medical facility in rural Minnesota were contacted by telephone. Of this group, 172 individuals (32.3%) responded that they were not under the care of an ophthalmologist; 117 (22.0%) individuals indicated that they had been seen by an ophthalmologist in the past, but that the last examination was more than two years ago

(mean, 4.9 years). The 172 patients who had no ophthalmologist were considered to be at high risk for ocular disease and they were invited to receive an eye examination; 145 diabetic subjects completed the examination. All patients were white, the average age was 54.1 years, and the average duration of diabetes was 6.2 years. The examination disclosed that 31 of 145 patients (21.4%) had nonproliferative diabetic retinopathy, seven (4.8%) had proliferative or preproliferative retinopathy, and four (2.8%) had diabetic macular edema.

The subjects ≥ to 35 years of age were also screened for cataract and glaucoma. Fourteen individuals (11.2%) had lens opacities and decreased visual acuity, 20 individuals (16.0%) had increased intraocular pressure, and six (4.8%) had glaucomatous optic disk changes.

This study indicates the high prevalence of sight threatening disease in diabetic patients. Ophthalmologists must educate internists, family practitioners, and diabetic patients about the importance of periodic routine ophthalmic examinations.—Michael A. Kass

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Criteria for diagnosis of Behçet's disease. International Study Group For Behçet's Disease* Lancet 335:1078, 1990.

BEHÇET'S DISEASE

A group of patients with Behçet's disease was studied to determine the optimal diagnostic criteria for the disease. Data from 914 patients with Behçet's disease were collected from 12 centers in seven countries. These data were compared to data from 97 patients who had recurrent oral ulceration caused by other diseases such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, or psoriatic arthropathy. Six different sets of diagnostic criteria were tested to determine the set that had the best sensitivity and specificity for the disease. The international study group concluded that for a diagnosis of Behçet's disease, patients must have at least three episodes of aphthous or herpetiform ulcerations in 12 months. Additionally, the patients must have two of the following four findings: recurrent genital ulceration; ocular findings such as anterior or posterior uveitis, cells in the vitreous, or

retinal vasculitis; skin lesions including erythema nodosum, pseudofolliculitis, or papulopustules; and positive pathergy test (a sterile pustule developing within 24 to 48 hours at the site of a needle puncture in the skin). These diagnostic criteria had a sensitivity of 95% and a specificity of 98%.—Michael A. Kass

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Local ocular compensation for imposed local refractive error. Miles, F. A.,* and Wallman, J. Vision Res. 30:339, 1990.

OCULAR DEVELOPMENT, EMMETROPIA

At hatching, a chick's eyes are normally slightly hyperopic, and over a period of weeks, gradually become emmetropic. Deprivation of form vision during this developmental period results in severe myopia, mainly caused by axial elongation of the vitreous chamber. One hypothesis is that deprivation of form vision inhibits a growth control mechanism that is visually mediated and that normally functions to match the size of the eye to its optical power.

Chicks were raised in a low-ceiling environment. The chicks became more myopic in the upper visual field than did chicks raised in a high-ceiling environment. The vitreous chamber in the chicks raised in a low-ceiling environment showed a selective elongation in the ventral region that was not seen in the eyes of chicks raised in a high-ceiling environment. The morphologic difference appeared adequate to account for the additional myopia in the low-ceiling chicks.

These results are consistent with the hypothesis of a visually mediated growth mechanism regulating the local refractive state across the entire visual field so that it matches the customary viewing conditions. This is similar to previous studies in birds showing that refractive errors in the lower visual field are appropriate for focusing the image of the ground on the retina, while the eye may be emmetropic at or above the horizontal meridian.—Michael A. Kass

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Effect on physician-scientists of the low funding rate of NIH grant applications. Movsesian, M. A.* N. Engl. J. Med. 322:1602, 1990

NATIONAL INSTITUTES OF HEALTH FUNDING

The National Institutes of Health provide funds that are crucial to physician-scientists and medical schools. As funds diminish many medical school departments may find that they cannot afford to hire or maintain staff members whose primary interest is research. In 1989, the success rates for new RO1 grants was 17.1% in the National Cancer Institute and 18.9% in the National Heart, Lung, and Blood Institute. The fiscal 1990 budget will enable the National Institutes of Health to fund 4,633 competitive grants, 667 fewer than fiscal 1989.

Since the average duration of a National Institutes of Health grant is 4.1 years, physician-scientists must go through three cycles—an initial review and two competitive renewals—in order to obtain funding for a ten-year period. At the National Institute on Aging, where the success rates for fiscal 1989 were 16.9% for new RO1 applications and 28.4% for competing RO1 renewals, the likelihood of a positive outcome on three successive reviews would be $0.169 \times 0.284 \times 0.284$ or 1.4%.

Investigators can increase their likelihood of success by submitting multiple applications. The chance of success is represented by $1 - F^n$, where F is each application's probability of failure and n is the number of applications submitted. Using the same assumptions for the National Institute on Aging, a minimum of 18 applications would be required over ten years to achieve approximately a 50% chance of funding over time. This assumes that only the investigator in question increases the number of applications.

There seems to be little enthusiasm within the federal government to increase expenditures for biomedical research. This has important implications for established investigators, but even more important implications for young physician-scientists who wish to begin a career in biomedical research.—Michael A. Kass

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Platelet hyperreactivity and prognosis in survivors of myocardial infarction. Trip, M. D.,* Cats, V. M., van Capelle, F. J. L., and Vreeken, J. N. Engl. J. Med. 322:1549, 1990.

MYOCARDIAL INFARCTION, PLATELET
HYPERREACTIVITY

We tested the hypothesis that an increase in spontaneous aggregability of platelets in vitro predicts mortality and coronary events in patients who have survived a recent myocardial infarction. A cohort of 149 survivors of infarction entered our study three months after the index infarction and was followed for five years. At entry and at intervals of six months, spontaneous platelet aggregation (SPA) was tested and graded as positive (aggregation within 10 minutes), intermediate (aggregation after 10 to 20 minutes), or negative (no aggregation within 20 minutes).

During follow-up, 6.4 percent (6 of 94) of the patients in the SPA-negative group died, as compared with 10.3 percent (3 of 29) in the SPA-intermediate group and 34.6 percent (9 of 26) in the SPA-positive group. As compared with the SPA-negative group, the SPA-intermediate group had a relative risk of death of 1.6 (95 percent confidence interval, 0.5 to 5.5) and the SPA-positive group had a risk of 5.4 (95 percent confidence interval, 2.2 to 13.4). At least one cardiac event (cardiac death or recurrent nonfatal myocardial infarction) occurred in 14.9 percent (14 of 94 patients) of the SPA-negative group, 24.1 percent (7 of 29) of the SPA-intermediate group, and 46.2 percent (12 of 26) of the SPA-positive group. A positive test result continued to have prognostic value throughout the five-year study.

We conclude that spontaneous platelet aggregation in vitro is a useful biologic marker for the prediction of coronary events and mortality in this low-risk group of survivors of a myocardial infarction. A causal relation is suggested but not proved by our study.—Authors' abstract

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Pathogenesis of laser-induced choroidal subretinal neovascularization. Miller, H.,* Miller, B., Ishibashi, T., and Ryan, S. J. Invest. Ophthalmol. Vis. Sci. 31:899, 1990.

SUBRETINAL NEOVASCULARIZATION, ARGON
LASER TREATMENT

Subretinal neovascularization can be induced in the subhuman primate by intense argon laser photocoagulation. This animal model was useful for studying macular degeneration as well as subretinal neovascularization in humans after therapeutic laser application. Thirteen cynomolgus monkeys each received eight argon laser photocoagulation burns at and around the macula. The treatment characteristics were 700 mW, 100-μm spot size, and 0.1-second duration. At various times after treatment the eyes were examined and then prepared for histologic study. The first day after photocoagulation there was disruption of the choroid, Bruch's membrane, and the retinal pigment epithelium. The phase of disruption was followed by an inflammatory response. Subsequently, newly formed choroidal tissue filled the wound and retinal pigment epithelial cells proliferated from the edges of the wound over the newly formed choroidal tissue. In lesions with minimal damage to the retinal pigment epithelium, closure of the wound was rapid and proliferating choroidal tissue did not reach the subretinal space. In contrast, in lesions with a large area of retinal pigment epithelial damage, coverage of the choroidal lesion was slow, fluid accumulated in the subretinal space, and pooling of fluorescein was noted on angiography.

These results indicate that the amount of damage to the choroid–Bruch's membrane–retinal pigment epithelium and the ability of the pigment epithelial cells around the damaged area to proliferate and restore its continuity determine the evolution of newly formed choroidal fibrovascular tissue into a subretinal membrane.—Michael A. Kass

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The need to reform personal injury law leaving scientific disputes to scientists. Sugarman, S. D.* Science 248:823, 1990.

SCIENTIFIC EVIDENCE, PERSONAL INJURY LAW

A professor of law at the University of California, Berkeley, examined the personal injury legal system and concluded that it requires

extensive reform. Personal injury cases often involve complex scientific issues that cannot be judged adequately by a lay jury. The author stated that in many cases, the jury is forced to choose between conflicting testimonies from expert witnesses whose scientific credibility they are unable to appraise. Despite these shortcomings, American tort law might be acceptable if it promoted socially desirable behavior on the part of manufacturers and professional groups. The author concluded that, to date, there is little evidence that tort law promotes public safety. He also stated that the tort system is spotty with some accident victims becoming millionaires while others receive no compensation. A high proportion of the money paid for liability insurance goes to lawyers' fees, brokers' fees, marketing expenses, insurer overhead, and insurer profits rather than to accident victims. Finally, the author stated the present tort system has other negative impacts such as inhibiting firms from undertaking new product development or inducing physicians to order unnecessary tests.

In contrast to the American system, in New Zealand there are no private lawsuits by accident victims. Victims can claim compensation from a national agency for income replacement, medical expenses, rehabilitation costs, and other losses. Seriously injured victims can obtain up to $NZ 27,000 for pain and permanent impairment. The New Zealand system is funded by contributions from employers, motorists, and general taxes. In 1991, New Zealand will implement a system so that individuals disabled by illness are on a par with those disabled by accident.—Michael A. Kass

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Acute angle-closure glaucoma following botulinum toxin injection for blepharospasm. Corridan, P.,* Nightingale, S., Mashoudi, N., and Williams, A. C. Br. J. Ophthalmol. 74:309, 1990.

ANGLE-CLOSURE GLAUCOMA, BOTULINUM, BLEPHAROSPASM

An 83-year-old woman received two 0.15-ml injections of botulinum toxin above each eye, and two 0.1-ml injections below each eye to relieve blepharospasm. Thirteen weeks later

the blepharospasm had recurred on the right side and the patient received two additional 0.1-ml injections above each eye. Three hours later the patient noted pain about the left eye associated with blurred vision, nausea, and vomiting. Despite these symptoms she did not seek medical help for three days. On examination the patient had visual acuity of light perception in the left eye with corneal edema and an intraocular pressure of 60 mm Hg. Gonioscopy was not possible in the left eye, but the right eye had very narrow angles. The patient underwent emergency medical treatment for angle-closure glaucoma, and then laser peripheral iridotomies in both eyes, and finally a trabeculectomy in the left eye.

Botulinum toxin acts to inhibit the release of acetylcholine at peripheral cholinergic synapses, sympathetic ganglia, and preganglionic and postganglionic nerve terminals of the parasympathetic nervous system. Patients systemically poisoned by botulinum toxin characteristically have middilated fixed pupils. Pupillary dilation could occur if botulinum toxin inhibits release of acetylcholine in the ciliary ganglion or the neuromuscular junction of the sphincter muscle of the iris. It seems prudent to assess the anterior chamber angle on all patients before treatment with botulinum toxin. Patients at risk for angle closure may need prophylactic laser iridotomies.—Michael A. Kass

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Association between Graves' ophthalmopathy and smoking. Shine, B., Fells, P., Edwards, O. M., and Weetman, A. P.* Lancet 335:1261, 1990.

GRAVES' OPHTHALMOPATHY, SMOKING

Graves' ophthalmopathy is an autoimmune disease that affects the extraocular muscles. It is unclear what factors cause some individuals with thyroid autoimmunity to develop overt ocular disease while other individuals have only subclinical ocular findings.

Questionnaires about smoking were returned by 85 patients with Graves' ophthalmopathy, 62 patients with thyrotoxicosis and subclinical eye findings, and 81 control subjects. The groups were similar in age, gender, and socioeconomic status. The patients with Graves'

ophthalmopathy had a significantly higher level of smoking (62% were current smokers) than the thyrotoxicosis group (27% were current smokers) or the controls (13.6% were current smokers).

Smoking may alter a variety of immunologic functions including peripheral blood T-cell phenotypes and function, production of acute-phase reactants, complement products, and interleukin-1. Such immunologic alterations may predispose to the development of clinical ocular disease in patients with thyroid autoimmunity.—Michael A. Kass

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The body-mass index of twins who have been reared apart. Stunkard, A. J.,* Harris, J. R., Pedersen, N. L., and McClearn, G. E. N. Engl. J. Med. 322:1483, 1990.

OBESITY, TWIN STUDY

Although recent studies have established the influence of genetic factors in human obesity, the extent of the genetic contribution is not clear. This was assessed in a Swedish study of 93 pairs of identical twins reared apart, 154 pairs of identical twins reared together, 218 pairs of fraternal twins reared apart, and 208 pairs of fraternal twins reared together. The intrapair correlation coefficients of the value for body-mass index (weight in kilograms divided by the square of the height in meters) of identical twins reared apart were 0.70 for men and 0.66 for women. These correlation coefficients were only slightly lower than those for twins reared together. These results suggest that genetic factors may account for as much as 70% of the variance in body-mass index. In contrast, childhood environment has little or no influence on body-mass index.—Michael A. Kass

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The prevalence of illicit-drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida. Chasnoff, I. J.,* Landress, H. J., and Barrett, M. E. N. Engl. J. Med. 322:1202, 1990.

PREGNANCY, ILLICIT DRUG USE

Florida is one of several states that have sought to protect newborns by requiring that mothers known to have used alcohol or illicit drugs during pregnancy be reported to health authorities. To estimate the prevalence of substance abuse by pregnant women, urine samples were collected from all pregnant women enrolled for prenatal care at five public health clinics in Pinellas County, Florida (n = 380) or at 12 private obstetric offices (n = 335). Each center was studied for a one-month period during the first half of 1989. Toxicologic screening for alcohol, opiates, cocaine and its metabolites, and cannabinoids was performed using an enzyme-multiplied immunoassay technique; all positive results were confirmed.

The overall prevalence of a positive result on the toxicologic tests of urine was 14.8%. There was little difference in the prevalence of positive results between women seen at the public clinics (16.3% positive) and those seen at the private offices (13.1% positive). The frequency of a positive result was also similar among white women (15.4%) and black women (14.1%). Black women had a higher prevalence of cocaine use (7.5% positive vs 1.8% for white women) whereas white women had a higher prevalence of cannabinoid use (14.4% positive vs 6.0% for black women).

During the six-month period of this study, 133 women in Pinellas County were reported for substance abuse during pregnancy. Despite the similar rates of substance abuse in the study, black women were reported at approximately ten times the rate of white women (P < .0001).—Michael A. Kass

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Changes in risk factors and the decline in mortality from cardiovascular disease. The Framingham Heart Study. Sytkowski, P. A.,* Kannel, W. B., and D'Agostino, R. B. N. Engl. J. Med. 322:1635, 1990.

CARDIOVASCULAR DISEASE, HYPERTENSION, CHOLESTEROL

A decline in mortality from cardiovascular disease over the past 30 years has been well

documented, but the reasons for the decline remain unclear. We analyzed the 10-year incidence of cardiovascular disease and death from cardiovascular disease in three groups of men who were 50 to 59 years old at base line in 1950, 1960, and 1970 (the 1950, 1960, and 1970 cohorts) in order to determine the contribution of secular trends in the incidence of cardiovascular disease, risk factors, and medical care to the decline in mortality.

The 10-year cumulative mortality from cardiovascular disease in the 1970 cohort was 43 percent less than that in the 1950 cohort and 37 percent less than that in the 1960 cohort (P = 0.04 by log-rank test). Among the men who were free of cardiovascular disease at base line, the 10-year cumulative incidence of cardiovascular disease declined approximately 19 percent, from 190 per 1000 in the 1950 cohort to 154 per 1000 in the 1970 cohort (0.10 < P < 0.20 by chi-square test), whereas the 10-year rate of death from cardiovascular disease declined 60 percent (relative risk for the 1950 cohort as compared with the 1970 cohort, 2.53; 95 percent confidence interval, 1.22 to 5.97).

Significant improvements were found in risk factors for cardiovascular disease among the men initially free of cardiovascular disease in the 1970 cohort as compared with those in the 1950 cohort, including a lower serum cholesterol level (mean ± SD, 5.72 ± 0.98 mmol per liter [221 ± 38 mg per deciliter], as compared with 5.90 ± 1.03 mmol per liter [228 ± 40 mg per deciliter]) and a lower systolic blood pressure (mean ± SD, 135 ± 19 mm Hg, as compared with 139 ± 25 mm Hg), better management of hypertension (22 percent vs. 0 percent were receiving antihypertensive medication), and reduced cigarette smoking (34 percent vs. 56 percent). We propose that these improvements may have had more pronounced effects on mortality from cardiovascular disease than on the incidence of cardiovascular disease in this population.

Our data suggest that the improvement in cardiovascular risk factors in the 1970 cohort may have been an important contributor to the 60 percent decline in mortality in that group as compared with the 1950 cohort, although a decline in the incidence of cardiovascular disease and improved medical interventions may also have contributed to the decline in mortality.—Authors' abstract

*New England Research Institute, 9 Galen St., Watertown, MA 02172.

Running, osteoarthritis, and bone density. Initial 2-year longitudinal study. Lane, N. E., Bloch, D. A., Hubert, H. B., Jones, H., Simpson, U., and Fries, J. F.* Am. J. Med. 88:452, 1990.

JOGGING, OSTEOARTHRITIS, BONE MASS

An estimated 15 million Americans exercise by running or jogging, which has raised concerns about the development of osteoarthritis in weight-bearing joints. The authors report the first two-year results of an eight-year prospective study of the effect of running on bone mass and the development of osteoarthritis.

Thirty-four members of a running club, aged 52 to 74 years, and 34 matched controls had roentgenograms of the hands, lateral lumbar spine, and knees as well as computed tomographic scans of the first lumbar vertebrae in 1984 and then again in 1986. The runners had greater bone density at baseline and continued to have greater density over the follow-up period. Individuals who stopped or greatly decreased running had a marked loss of bone mineral from the spine. Roentgen scores of osteoarthritis increased equally in both runners and controls over the follow-up period. The exception to this finding was that female runners had more spur formation noted in knee roentgenograms than did control subjects. The significance of this finding is unclear at present. The data suggest no obvious deleterious effect of long-term running on the development of osteoarthritis and a probable protective effect on bone mass.—Michael A. Kass

*Stanford University Medical Center, HRP Building, Room 109, Stanford, CA 94305.

NEWS ITEMS

American Association for the History of Medicine: 1991 Meeting

The American Association for the History of Medicine will hold its 1991 meeting in Cleveland, Ohio, May 1–4, 1991. The deadline for submission of abstracts for papers is Oct. 15, 1990. For further information, write to Dr. Gerald N. Grob, Chair, AAHM Program Committee, Institute for Health Policy, 30 College Ave., Rutgers University, New Brunswick, NJ 08903; telephone (908) 932-8377.

Contact Lens Association of Ophthalmologists: 1991 Annual Meeting

The Contact Lens Association of Ophthalmologists: 1991 Annual Meeting will be held Jan. 13–16, 1991, at Caesars Palace in Las Vegas, Nevada. For further information, write Meetings Registrar, CLAO, 523 Decatur St., Suite One, New Orleans, LA 70130-1027; telephone (504) 581-400; fax (504) 581-5884.

Georgetown University Medical Center: Conference on Policy Evolution in Ophthalmology

The Conference on Policy Evolution in Ophthalmology, sponsored by the Program on Technology and Health Care and the Worthen Center for Eye Care Research of Georgetown University Medical Center will be held Dec. 4 and 5, 1990, in Washington, D.C. For further information, write Marcia Marshall, Program on Technology and Health Care, Department of Community and Family Medicine, Georgetown University Medical School, 3900 Reservoir Rd. N.W., Washington, DC 20007; telephone (202) 687-7775.

Hawaiian Eye Foundation: 12th Annual Royal Hawaiian Eye Meeting

The Hawaiian Eye Foundation: 12th Annual Royal Hawaiian Eye Meeting will be held Jan. 19–26, 1991, at the Hyatt Waikoloa on the Big Island of Hawaii. For further information, write Mary Charles & Associates, 2334 S. King St., Suite 205, Honolulu, Hawaii 96826; telephone (808) 942-9655.

Manhattan Eye, Ear & Throat Hospital: LuEsther T. Mertz Vitreous-Retina-Macula Lectures

The LuEsther T. Mertz Vitreous-Retina-Macula Lectures will be held Oct. 16, 1990, Jan. 15, 1991, and March 19, 1991, at the Manhattan Eye, Ear & Throat Hospital in New York City. For further information, write Kimberly Corbin, Course Coordinator, Department of Ophthalmology, MEETH, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761.

Manhattan Eye, Ear & Throat Hospital: Glaucoma Seminar

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold a Glaucoma Seminar Nov. 10, 1990, in New York City. For further information, write Kimberly Corbin, Course Coordinator, Department of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761.

Maryland Society of Eye Physicians and Surgeons: Ocular Plastic Surgery—Current Concepts and Techniques

The Maryland Society of Eye Physicians and Surgeons: Ocular Plastic Surgery—Current Concepts and Techniques conference will be held Oct. 1, 1990, in Columbia, Maryland. For further information, write Terry Slade Young, 11 S. Paca St., Suite 303, Baltimore, MD 21201; telephone (301) 328-2399; fax (301) 328-8514.

Phillips Eye Institute

Current Trends in Ophthalmology will be presented by the Phillips Eye Institute at the Hotel Sofitel, Minneapolis, Oct. 6, 1990. Advanced Phacoemulsification and Anterior Segment Surgery Course will be conducted at the Phillips Eye Institute Center for Teaching and Research, Minneapolis, Oct. 7 and 8, 1990. For

information concerning either course, write Mary Strazz, Phillips Eye Institute, 2215 Park Ave. S:, Minneapolis, MN 55404; telephone (612) 336-5650.

St. Luke's Medical Center: 17th Annual Frontiers in Ophthalmology

The St. Luke's Medical Center: 17th Annual Frontiers in Ophthalmology sponsored by the Prentice Eye Institute and St. Luke's Medical Center will be held Feb. 21–23, 1991, in Scottsdale, Arizona. For further information, write Christine Campbell, Campbell Meeting Management; 1419 E. Divot Dr., Tempe, AZ 85283; telephone (602) 820-7027.

Association for Research in Vision and Ophthalmology: New Trustees

The Association for Research in Vision and Ophthalmology new trustees are Richard A. Thoft, David L. Guyton, and Leo T. Chylack, Jr.

Association for Research in Vision and Ophthalmology: 1991 Award Winners

The Association for Research in Vision and Ophthalmology 1991 Award Recipients include the following: Robert B. Nussenblatt and Waldon B. Wacker, Proctor Medal; Richard F. Brubaker, Friedenwald Award; Bradley R. Straatsma, Mildred Weisenfeld Award for Excellence in Ophthalmology; and Jay S. Pepose, Cogan Award.

Personals

Andrew W. Lawton

Andrew W. Lawton has been named the Director of the Neuro-ophthalmology Service of the Louisiana State University Eye Center, LSU Medical Center School of Medicine in New Orleans.

Oliver D. Schein

Oliver D. Schein is the recipient of a career development fellowship awarded by Merck Company Foundation and the Society for Epidemiologic Research. He will pursue studies of cataracts and their treatment in the United States and developing countries. The $190,000 three-year fellowship will support Dr. Schein's research at the Dana Center for Preventive Ophthalmology at John Hopkins.

John D. Sheppard

John D. Sheppard has been named Director of Residency Training for the Department of Ophthalmology at the Eastern Virginia Medical School.

Alfred Sommer

Alfred Sommer, a distinguished Johns Hopkins ophthalmologist, epidemiologist, and specialist in international health, has been appointed dean of the Johns Hopkins University School of Hygiene and Public Health, effective Sept. 1, 1990.

THE DRY EYE SPECIALISTS

Introducing Two *New* Punctum Plug Kits

U.S. Patent No. 3,949,750
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For use in the treatment of keratitis sicca by reversible occlusion of the punctum and canaliculus.
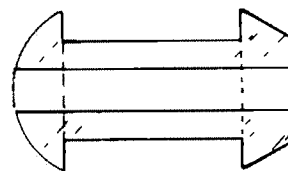
LARGE SIZE # 0009

25% wider diameter than Standard Size Plug for patients with lax lids and large puncta, featuring Medium Size Plug dome.
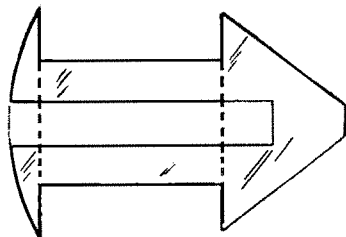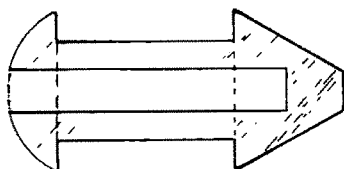
2.8mm Length

PUNCTUM FLOW CONTROLLER # 0008

Standard Size Plug with open nose to modulate the flow of lacrimal fluid through a punctum and canaliculus.

2.3mm Length

Complementing our growing family of Eagle Vision-Freeman™ Punctum Plug Kits.

STANDARD SIZE # 0001

2.8mm Length

MEDIUM SIZE # 0003

New improved nose design for easier insertion.
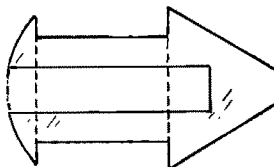
2.0mm Length

SMALL SIZE # 0004

1.6mm Length

Dilator

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Inserter

Introduction of punctum plug held in place by inserter end of dilator/inserter instrument, using Lid Fixation Forceps.

EACH KIT CONTAINS:

2-Punctum Plugs of medical grade silicone
1- Dilator/inserter combination instrument
Physician instructions

Products #0001, #0003 and #0004 also available in **MULTI-PACK KITS** with 10 Punctum Plugs each.

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—available as a separate item

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